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DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
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MEMORANDUM

DATE: November 5, 1999

TO: File, NDA 21-038

FROM: Bob A. Rappaport, M.D.
Deputy Director, DACCADP
Team Leader, Anesthetic Drug Group

RE: Supervisory Review of NDA 21-038, Dexmedetomidine HCl

BACKGROUND:

NDA 21-038, Dexmedetomidine HCl, was submitted by Abbott Laboratories Inc. on December 18, 1998. Dexmedetomidine is a potent and highly selective α-2-adrenoreceptor agonist. The sponsor claims that their product produces titratable, predictable sedation in an ICU setting, from which patients are easily arousable and cooperative. The sponsor also claims that their product provides improved analgesia in the postoperative ICU setting. The α-2-adrenoreceptor agonist detomidine was developed for use as a sedative/analgesic in horses and cattle and was registered for marketing in Finland in 1983. Medetomidine, launched in 1987 in Scandinavia, was a more selective α-2-adrenoreceptor agonist used as a sedative/analgesic in cats and dogs. It was approved for veterinary use in the US in 1997. The sedative and analgesic activity of medtomidine are believed to reside predominantly in its dextroenantiomer dexmedetomidine. The enantiomer was first synthesized by Farmos Group in Finland in 1986. Numerous perioperative indications have been evaluated since that time. Farmos merged with Orion Corp. in 1990, and Orion licensed the injectable dosage form of dexmedetomidine for clinical use to Abbott Laboratories in 1994.

Orion conducted 56 clinical trials of dexmedetomidine with various modes of administration including rapid intravenous infusion, continuous intravenous infusion,

intramuscular injection, as well as transdermal and oral administration. Abbott initiated its own clinical development program and completed 21 studies (13 Phase I and 8 Phase II/III) in the US, Canada and Europe. They also completed 2 studies in Japan: a Phase I safety and pharmacokinetic study of rapid infusion in 9 healthy males, and a Phase II safety and dose response study of rapid infusion in 109 patients. The sponsor reported that the case report forms for these 2 studies were unavailable and they did not include the data in the ISS database.

The clinical studies of the effectiveness and safety of this new formulation have been reviewed [submitted August 29, 1999] by Charles Cortinovis, M.D. Dr. Patricia Hartwell contributed two addenda [submitted September 13, 1999 and October 27, 1999] reviewing safety data in the original application, a supplementary safety package, and the 120-Day Safety Update. The application has also been reviewed by Jonathan Ma, Ph.D. (biostatistics), Suresh Doddapaneni, Ph.D. (clinical pharmacology and biopharmaceutics), Harry Geyer, Ph.D. (pharmacology/toxicology), Michael Theodorakis, Ph.D. (chemistry), and BeLinda A. Hayes, Ph.D. (abuse liability). In this memo, I will briefly review the effectiveness and safety data summarized in the primary clinical review, as well as any relevant information found in the primary reviews from the other disciplines, and make appropriate recommendations for action on the NDA.

EFFECTIVENESS:

Evidence of efficacy has been submitted in two clinical studies W97-245 and W97-246.

Study W97-245:

This was a randomized, double blind, placebo-controlled, parallel group study conducted at 33 centers in Canada and Europe. The Study consisted of two parts. Part I was an open-label evaluation of dexmedetomidine in up to 4 patients per site. This portion of the study was designed to allow the investigators to become familiar with the observed clinical effects of dexmedetomidine prior to starting the double-blind portion of the study. Patient data from Part I was not included in the efficacy analyses.

In Part II of the study, adult postoperative patients who required a minimum of 6 hours of ventilation and sedation in the ICU setting were randomized to either dexmedetomidine or placebo for sedation. Within one hour of admission to the ICU, patients were

administered a loading dose 6.0 µg/kg/hour over a 10 minute period, followed by a maintenance infusion of 0.4 µg/kg/hour. The infusion rate could be adjusted by increments of 0.1 µg/kg/hour in order to maintain a Ramsay Sedation Score[1] of 3 or higher. However, it was required that the rate be maintained between 0.2 and 0.7 µg/kg/hour. Following extubation, the infusion rate was adjusted to achieve a Ramsay Sedation Score of 2 or above. Study drug infusion was continued for at least 6 hours after extubation and, at the discretion of the investigator, up to a maximum of 24 hours total study drug infusion.

Rescue medications were limited to midazolam for sedation and morphine for pain. After extubation, paracetamol was administered when clinically indicated. When the investigators judged that there was need for an increase in sedative medication, they were to first adjust the maintenance dose of dexmedetomidine. Midazolam was administered as bolus doses of 0.02 mg/kg. Using the Ramsay Sedation Score, the patient was assessed prior to and 10 minutes after every rate change in study drug or administration of midazolam. If the patient required 3 bolus doses of midazolam within any 2 hour period, after appropriate adjustments of the study drug infusion rate, further midazolam was administered as a continuous infusion at 0.01 to 0.02 mg/kg/hour.

The need for analgesic administration was assessed either by direct communication with the patient regarding pain, or by the presence of abnormal autonomic signs such as sweating, tachycardia and hypertension. Morphine was administered for pain as 2-mg intravenous boluses.

The protocol specified primary efficacy parameter was the total dose of midazolam in milligrams administered during the period that the patient was intubated. The efficacy analysis was based on the Intent to Treat [ITT] population and analysis on the Evaluable population was also performed. A second primary efficacy endpoint was analyzed based on a recommendation made by the Division biostatistician, Dr. Permutt, at a development meeting with the sponsor. This endpoint was a comparison of the numbers of patients who fell into one of the following three categories of midazolam use:

1. No dose (0 mg)
2. Subtherapeutic dose (0-4 mg)
3. Therapeutic dose (>4 mg)

This outcome measure was not specified in any amendment to the protocol. However, the analysis was undertaken prior to breaking the study blind.

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[1] 6 = asleep, no response
5 = asleep, sluggish response to light glabellar tap or loud auditory stimulus
4 = asleep but with brisk response to light glabellar tap or loud auditory stimulus
3 = patient responds to commands
2 = patient cooperative, oriented, and tranquil
1 = patient anxious, agitated, or restless

Secondary efficacy parameters listed in the protocol for this study included[2]:

1. Use of morphine for pain – as assessed by total dose used with dexmedetomidine as compared to placebo (mg/hr)
2. Use of paracetamol for pain after extubation – as assessed by total dose used with dexmedetomidine compared to placebo (mg/hr)
3. Time to extubation – measured as time of arrival in ICU until time of extubation

However, the secondary efficacy parameters listed in the study report were:

1. Total dose of midazolam during study drug administration
2. Total dose of morphine during study drug administration
3. Total dose of morphine by time period
4. Ramsay Sedation Score
5. Ratio[3] of Ramsay Sedation Score of "1" during study drug administration
6. Time to extubation and weaning duration
7. Nurses' and patients' assessment

These changes in secondary outcome measures were not specified in any amendment to the protocol.

Results:

Eighty-six patients were enrolled and 85 treated in Part I of the study.

In Part II of the study, 178 patients were randomized to dexmedetomidine and 175 to placebo. All patients were administered study drug and comprised the ITT population. Two dexmedetomidine treated and 6 placebo patients were excluded from the Evaluable patient set.

Dr. Cortinovis' Table 4 [page 22 of his review], reproduced below, summarizes the patient disposition:

[2] This information differs from that documented by Dr. Cortinovis in the medical officer's review and by Dr. Ma in the Statistician's review. It is based on documentation provided by Dr. Patricia Hartwell who examined the original documents at my request.

[3] The ratio is the proportion of assessments that equal 1 divided by the total number of assessments for the patient.

Table 1.

	Placebo	Dexmedetomidine
Intent to Treat Patients (All Treated)	175	178
Non-Evaluable patients	6	2
Evaluable Patients	169	176
Reasons for Non-Evaluability (Patient Numbers)*		
Insufficient Study drug therapy	1001,4104	1806
Insufficient Intubation	1001,11705	1806
Received disallowed medication	1303,6004, 7601	6106

* Patients could have had more than one reason for non-evaluability
Modified Sponsor's Table 8.1a Vol. 8/10-62-73

Nine patients in the dexmedetomidine group and 10 in the placebo group were discontinued from the study prematurely. Each of these patients discontinued due to adverse events.

Primary Efficacy Analyses:

1. Dexmedetomidine patients required statistically significantly less midazolam compared to the placebo treated patients in both the ITT and Evaluable patient analyses. Dr. Cortinovis' Table 8, page 25 of his review, summarizes these results and is reproduced below:

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