CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-038

MEDICAL REVIEW(S)

N21038 on #21-038 HFD-170 K1.2

N21038

1.1.2

DRUG NAME: Precedex (dexmedetomidine hcl injection)

RLC 12/28/99

APPLICANT: ABBOTT LABORATORIES

CHEMICAL & THERAPEUTIC CLASS:1S

Review Cycles

Review Cycle: 1 **Submission Date:12-18-98** **Receipt Date:12-18-98** **Goal Date:12-18-99** **Action:AP**	**Review Cycle: 2** **Submission Date:** **Receipt Date:** **Goal Date:** **Action:**
Review Cycle: 3 **Submission Date:** **Receipt Date:** **Goal Date:** **Action:**	**Review Cycle: 4** **Submission Date:** **Receipt Date:** **Goal Date:** **Action:**

CORE REVIEW TEAM MEMBERS

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ABUSE LIABILITY: BeLinda A. Hayes, Ph.D.
MICROBIOLOGIST: Patricia Hughes, Ph.D.

Volume 2 of 4

Administrative volume #(s): 1
Clinical volume #(s): 2
CMC volume #(s): 3
Pharmacology/Toxicology volume #(s): 4

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Application #21-038

Drug Name: Precedex (dexmedetomidine Hydrochloride injection), 2 mL ampule/2 mL vial, 100 mcg/mL

Applicant: Abbott Laboratories Chem./Ther. Type:1S

CSO/PM: Susmita Samanta Phone: 301-827-7410 HFD-170

Original Application Date: December 18, 1998 Original Receipt Date: December 18, 1998

CURRENT USER FEE GOAL DATE: December 18, 1999 DateTableofContentsCompleted:9/13/99

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ADDITIONAL NOTES:

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

HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857
Tel:(301) 827-7410

MEMORANDUM

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

Division File: NDA # 21-038

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

/S/

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.

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.

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

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

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%).

Summary of Treatment-Emergent Adverse Events Occurring in >1% of Dexmedetomidine patients in Phase II/III Continuous Infusion ICU Sedation Studies[2]		
Adverse Event	Randomized dexmedetomidine (N=387)	Placebo N=379
Hypotension	84 (22%)*	16 (4%)
Hypertension	47 (12%)*	24 (6%)
Bradycardia	20 (5%)*	6(2%)
Mouth Dry	13 (3%)	4 (1%)
Nausea	16 (4%)	20 (5%)

*Statistically significant difference between randomized dexmedetomidine and placebo patients $p \leq 0.05$
Data source 2.2.5.5

Abnormal laboratory findings, which might have been anticipated from the preclinical studies, such as elevated LFTs and glycosuria, were not borne out in laboratory testing.

There are no safety data in pediatric patients. The sponsor will be required to study this product in children from birth to 16 years of age as a Phase 4 commitment.

Approximately 500 patients over 65 years of age have been studied in this NDA. An additional analysis of patients over 75 years has been requested of the sponsor with comparison of adverse events by age, separating the elderly by >65 to 75 and >75 years of age. This will be undertaken in an effort to assess whether dosage adjustment may be needed in the very elderly patients based on anticipated PD differences associated with sedative agents.

Abuse Potential

Dexmedetomidine might be expected, based on its clinical pharmacological effects and its similarity to clonidine[3], to have some abuse liability. Indeed animal studies indicate that there are some reinforcing properties. Reinforcing behavior in primates was elicited by dexmedetomidine 1.0 µg/kg/dose >saline and equivalent to saline at 0.0625 µg/kg/dose. At a dose of 0.25 µg/kg/dose dexmedetomidine produced reinforcing behavior comparable to pentazocine (CIV). Dexmedetomidine also has been shown to attenuate morphine withdrawal; suggestive but not conclusive evidence for dependence liability. A mild withdrawal syndrome has been described in rodents after 7 days of treatment.

Extensive receptor binding studies using standard radioligands were presented in the NDA, demonstrating very high affinity for the α-adrenergic receptors and moderate affinity for the serotonergic receptors. Binding at the opiate receptors was negligible. Comparative binding to relevant controlled substances was not provided.

[2] After Sponsor's Table 21 ISS 8/10-239-65

[3] Clonidine is not currently controlled in the CSA. There have been reports of abuse with clonidine, mostly of reports of opiate addicts using clonidine to suppress withdrawal symptoms rather than for its psychotropic effects.

On balance, the available studies suggest an abuse potential lower than some products controlled in schedule IV or as low as some not controlled at all. I do not agree with the controlled substances evaluation team that this product should not be scheduled due to lack of information, but rather that the available information suggests a rather low potential for abuse. Furthermore the clinical setting in which it will be used, limited to hospital intensive care units, reduces that potential. Continued vigilance is indicated, nevertheless, for any actual diversion and abuse that might occur in the post approval setting, so that appropriate measures can be taken to control this substance if needed. There have been to date no reports of diversion or abuse of medetomidine approved in 1997.

Biopharmaceutics

The ADME of dexmedetomidine has been fairly well studied, but some unanswered questions remain that may be very relevant to long term infusion. For example, it is has been demonstrated that there is almost no accumulation of parent drug, following IV bolus administration, and that there is nearly complete biotransoformation. The fate of the metabolites, however, has not been well characterized. Biotransoformation includes direct N-glucuronidation (two major metabolites, total of 34%) and CYP 2A6-mediated metabolism (three additional metabolites, 14%), and N-methylation (three metabolites, 18%). There are additional urinary metabolites that have not been identified yet. Dexmedetomidine is about 94% protein-bound.

Evaluation of dexmedetomidine in patients with renal failure demonstrated no change in dexmedetomidine PK with severe renal failure following a single dose, but there is no information about the possible accumulation of metabolites when dexmedetomidine is infused continuously, particularly for long periods of time. The bulk of elimination of metabolites is thought to be renal. Therefore, this information should be obtained in Phase 4 in anticipation of more prolonged infusion in patients with renal insufficiency.

Hepatic impairment affected the PK of dexmedetomidine as expected, and the appropriate adjustments for patients with mild, moderate and severe hepatic impairment will be included in the package insert.

There was no effect of age on the pharmacokinetics of dexmedetomidine, although only 20 elderly volunteers, ranging from 66 to 83 years (mean, 72) were evaluated. The possibility of pharmacodynamic differences increasing with increasing age were not examined, but should be looked at more closely in Phase 4, as sedative/hypnotics have a tendency to result in more significant safety problems (hypotension, confusion, respiratory depression) in the elderly. Dexmedetomidine has not been evaluated in the pediatric population.

Interaction studies with a spectrum of anesthetics *in vivo* such as alfentail, midazolam, propofol and isoflurane did not indicate interactions when added to dexmedetomidine or to alfentail, midazolam, propofol or rocuronium when dexmedetomidine was added.

Chemistry and Manufacturing

Dexmedetomidine is the dextro-enantiomer of medetomidine (4-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole hydrochloride) and it is manufactured by separation of the isomers from the racemic mixture. Preparation and characterization of the drug substance, levels of impurities including optical purity (levo-enantiomer limited to ≤1%) have all been judged acceptable. Stability data on the bulk drug substance and regulatory specifications were also deemed acceptable.

The drug product is a sterile aqueous solution of dexmedetomidine for intravenous infusion upon further dilution. The formulation consists of dexmedetomidine HCl (the active ingredient) and sodium chloride and water for injection. The drug product is prepared using standard methods, has undergone stability testing (undiluted) under ICH storage conditions generating data to support a 2-year shelf life, and has been shown to be stable in light. Sterility of the drug product is achieved through aseptic fill and terminal sterilization by autoclave. The process and data have been reviewed by microbiology and found to be acceptable.

The drug product is prepared for use by diluting it with sterile 0.9% sodium chloride solution for injection after which it is stable for 24 hours.

Compatibility data are provided with commonly used IV solutions, drugs (vasoactive agents, muscle relaxants, sedatives, narcotics and plasma substitute), tubing, and syringes commonly used for administration of IV drugs. It was observed that dexmedetomidine has the potential for adsorption onto certain types of natural rubber. This will be noted in the package insert, advising use with synthetic components or coated natural rubber components.

A suitable trade name has not yet been selected for the drug product to which the Agency agrees.

Data Integrity

All questions related to data integrity were resolved during the course of review and inspection, including questions about some unreported deaths, randomization errors and protocol violations that were not reported. DSI inspections were conducted, and aside from some reports of careless errors in recordkeeping there was no evidence to suggest

that the data on which the conclusions and recommendations for this NDA will be based have significant problems.

Comments:
There is adequate evidence to support the efficacy and safety of dexmedetomidine to approve it for ICU sedation by continuous infusion for 24 hours. It is anticipated that there will be increasing demand for more prolonged use of this product once it is approved. In addition to collecting additional safety data on prolonged use, there should be a better characterization of the activity, toxicity and fate of the metabolites.

Additional data should be obtained for safe use at the extremes of age—pediatric dosing, pharmacokinetics and safety should be obtained. Geriatric pharmacodynamic/safety data in the very elderly >75 years should also be generated or existing data analyzed.

Once the metabolic profile is better established with multiple dosing, its safety should be evaluated in patients with renal failure.

Surveillance for possible diversion and abuse can be done through the existing mechanisms such as Medwatch, SAMHSA's DAWN database, and DEA reports.

Phase 4 Commitments
The focus of the dexmedetomidine development plan was short-term ICU sedation in adults. It is quite clear that this product will not have use limited to this population, and therefore the following phase 4 commitments will be requested of the sponsor in an effort to obtain safety data in more extended ICU infusion, in pediatric patients and in the elderly.

Nonclinical studies

1. A two-week study in dogs with a 2-week recovery phase should evaluate general toxicology of prolonged infusion of dexmedetomidine and the effect of chronic infusion on HPA axis.
2. A second study should evaluate changes in drug metabolism following two weeks of infusion.
3. A third study should evaluate the potential toxicity of human major metabolites which are absent in rats and dogs.

Clinical Studies

1. **Pediatrics**: Studies to obtain an indication for sedation in pediatric patients from birth to 16 years of age in the ICU setting. The development plan should include pharmacokinetics and safety in pediatric patients from birth to 16 years, and efficacy data designed at determining appropriate dosage regimens.
2. **Geriatrics:** Further studies are needed to evaluate the safety v. differential toxicity of dexmedetomidine in very elderly patients, as has been described with other sedative/hypnotic drug products.
3. **Longer-term infusion** studies should include safety and pharmacokinetics.

4. **Renal Impairment**: Additional data are needed to examine the potential accumulation of dexmedetomidine metabolites upon continuous infusion in patients with renal impairment.

It is expected that a reasonable timeline for submission of the protocols might be approximately 6 months from approval; and completion of these studies, approximately 2 years.

Recommended Action: Approval of dexmedetomidine HCl as an adjunctive medication for ICU sedation.

APPEARS THIS WAY
ON ORIGINAL

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)443-3741

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:

Table 2. Total Dose of Midazolam (mg) During Intubation

	Placebo	Dexmedetomidine	Treatment Effect p-Value*
Intent to Treat Patients (N)	175	178	
Mean ± SEM	18.61±4.02	4.83±1.43	0.0011
Evaluable Patients (N)	169	176	
Mean ± SEM	18.46±4.14	4.56±1.42	0.0014

* p-value from ANOVA
SEM = Standard Error of Mean
Modified Sponsor's Table 8.2a Vol. 8/10-62-74

2. Statistically significant differences were observed between the treatment groups in both the ITT and Evaluable analyses, with the majority of the dexmedetomidine treated patients requiring no midazolam compared to the majority of placebo patients who required greater than 4 mg of midazolam. Dr. Cortinovis' Table 9, page 25 of his review, summarizes these results and is reproduced below:

Table 3. Total Dose Categories of Midazolam During Intubation

	Placebo	Dexmedetomidine	Treatment Effect p-Value*
Intent-to-Treat Patients (N)	175	178	<0.001
0 mg	43(25%)	108(61%)	
>0mg to 4 mg	34(19%)	36(20%)	
>4 mg	98(56%)	34(19%)	
Evaluable Patients (N)	169	176	<0.001
0 mg	43(25%)	107(61%)	
>0 mg to 4 mg	32(19%)	36(20%)	
> 4 mg	94(56%)	33(19%)	

* p-value from chi-square
Modified Sponsor's Table 8.2b Vol. 8/10-62-75

Secondary Efficacy Analyses:

Their were no differences in any of the analyses when performed on either the ITT or Evaluable patient data sets. The following table, based on Dr. Ma's Table 3.3, page 6 of his review, summarizes the results for six of these analyses:

Table 4.

	Placebo N = 175 Mean ± SEM*	Dexmedetomidine N = 178 Mean ± SEM	p-value Treatment Effect
Total dose of midazolam during drug administration (mg/hour)	1.19 (0.23)	0.29 (0.07)	0.0001
Total dose of morphine during drug administration (mg/hour)	0.83 (0.07)	0.47 (0.06)	<0.0001
Total dose of morphine during 0 to 6.5 hours (mg)	8.5 (0.79)	4.9 (0.56)	<0.0001
Total dose of morphine during 6.5 to end (mg/hour)	0.42 (0.08)	0.24 (0.05)	0.042
Ramsay Sedation Score AUC during drug administration	3.3 (0.05)	3.6 (0.05)	<0.0001
Ratio of Ramsay Sedation Score of 1 during drug administration (%)	7 (0.8)	3 (0.5)	<0.0001

*SEM = Standard Error of Mean

As noted by Dr. Ma in his review, the Ramsay Sedation Score itself (AUC) was not a useful endpoint to consider as, for both groups, dose titration and rescue medication were used to maintain the patients at a specified level of sedation indicated by the Ramsay Score. However, a smaller ratio of Ramsay score of 1, for any particular patient, might indicate less anxiety during the treatment period. Statistically significant center effects were noted for most secondary endpoints indicating that patients in different countries either required and/or were administered differing amounts of sedative and analgesic medications.

The following additional secondary endpoints were discussed by Dr. Cortinovis in his review:

Time to extubation and weaning duration:

No statistically significant differences were noted in time to readiness for extubation or actual extubation, when that time was measured either from ICU arrival or start of study drug. No statistically significant differences were found between the treatment groups for median duration of weaning.

Nurses' and patients' assessment

Dexmedetomidine treated patients had a statistically significantly lower patient management index [defined on page 30 of Dr. Cortinovis' review] score compared with

placebo treated patients. However, the actual numerical differences were not likely to be clinically relevant, according to Dr. Cortinovis.

Patient satisfaction survey

The dexmedetomidine treated and placebo patients rated similarly their present experience with sedation compared to prior experienees, their comfort during the ICU sedation, their remembrance of pain, discomfort from breathing tube, people and noise, and whether or not they would have the same sedative treatment in the future. However, 61% of dexmedetomidine treated patients compared to 52% of placebo patients rated their overall experience as "better than expected."

Data Integrity:

The Division of Scientific Investigations' [DSI] Clinical Inspection Summary for this application notes that one of the two pivotal study sites inspected by DSI was found to have protocol violations which may compromise some of the data arising out of that site. That site in Study W97-245 enrolled 5 out of 45 patients out of sequence; and one of those five subjects appeared to be a seven year old child who did not meet the inclusion criterion for age. DSI has requested clarification of the discrepancies and recommends that, until the matters are clarified and found to be satisfactory, we not use the data from those five subjects in support of the application.

Dr. Thomas Permutt, biostatistics teamleader, has reviewed the data and the DSI recommendations and has concluded that removal of the data from those five patients would not affect the outcome of the efficacy analyses.

Study W97-246:

This was a randomized, double blind, placebo-controlled, parallel group study conducted at 36 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[4] 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 maximum of 24 hours total study drug infusion.

Rescue medications were limited to propofol 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. Propofol 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 propofol. If the patient required 3 bolus doses of propofol within any 2 hour period, after appropriate adjustments of the study drug infusion rate, further propofol was administered as a continuous infusion at 0.5 to 4.0 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 propofol 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 propofol use:

1. No dose (0 mg)
2. Subtherapeutic dose (0-50 mg)
3. Therapeutic dose (>50 mg)

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

[4] 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[5]:

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 propofol 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[6] 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:

Ninety-three patients were enrolled and 92 treated in Part I of the study.

In Part II of the study, 203 patients were randomized to dexmedetomidine and 198 to placebo. All patients were administered study drug and comprised the ITT population. Three dexmedetomidine treated and 7 placebo patients were excluded from the Evaluable patient set.

Dr. Cortinovis' Table 18 [page 44 of his review], reproduced below, summarizes the patient disposition:

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ON ORIGINAL

[5] 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.

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

Table 5.

	Placebo	Dexmedetomidine
Intent to Treat Patients (All Treated)	198	203
Non-Evaluable patients	7	3
Evaluable Patients	191	200
Reasons for Non-Evaluability (Patient Numbers)		
Insufficient Intubation	1	N/A
Received disallowed medication	5	3
Enrolled twice	1	N/A

Modified Sponsor's Table 8.1a Vol. 8/10-86-73

Fourteen patients in the dexmedetomidine group and 8 in the placebo group were discontinued from the study prematurely. Most of these patients discontinued due to adverse events.

Primary Efficacy Analyses:

1. Dexmedetomidine patients required statistically significantly less propofol compared to the placebo treated patients in both the ITT and Evaluable patient analyses. Dr. Cortinovis' Table 22, page 47 of his review, summarizes these results and is reproduced, with modifications, below:

Table 6. Total Dose of Propofol (mg) During Intubation

	Placebo	Dexmedetomidine	Treatment Effect p-Value*
Intent to Treat Patients (N)	198	203	
Mean ± SEM	513±55.58	72±17.51	<0.0001
Evaluable Patients (N)	191	200	
Mean ± SEM	505±56.40	73±17.76	<0.0001

* p-value from ANOVA
SEM = Standard Error of Mean
Modified Sponsor's Table 8.2a Vol. 8/10-86-73

2. Statistically significant differences were observed between the treatment groups in both the ITT and Evaluable analyses, with the majority of the dexmedetomidine treated patients requiring no propofol compared to the majority of placebo patients who required greater than 50 mg of propofol. Dr. Cortinovis' Table 24, page 48 of his review, summarizes these results and is reproduced, with modifications, below:

Table 7. Total Dose Categories of Propofol During Intubation

	Placebo	Dexmedetomidine	Treatment Effect p-Value*
Intent-to-Treat Patients (N)	198	203	<0.001
0 mg	47(24%)	122(60%)	
> 0mg to 50 mg	30(15%)	43(21%)	
> 50 mg	121(61%)	38(19%)	
Evaluable Patients (N)	191	200	<0.001
0 mg	46(24%)	120(60%)	
>0 mg to 50 mg	30(16%)	42(21%)	
> 50 mg	115(60%)	38(19%)	

* p-value from chi-square
Modified Sponsor's Table 8.2b Vol. 8/10-86-74

Secondary Efficacy Analyses:

Their were no differences in any of the analyses when performed on either the ITT or Evaluable patient data sets. The following table, based on Dr. Ma's Table 3.6, page 10 of his review, summarizes the results for six of these analyses:

Table 8.

	Placebo N = 198 Mean ± SEM*	Dexmedetomidine N = 203 Mean ± SEM	p-value Treatment Effect
Total dose of midazolam during drug administration (mg/hour)	39 (4.1)	5.3 (1.2)	<0.0001
Total dose of morphine during drug administration (mg/hour)	0.89 (0.07)	0.43 (0.05)	<0.0001
Total dose of morphine during 0 to 6.5 hours (mg)	8.5 (0.64)	4.1 (0.47)	<0.0001
Total dose of morphine during 6.5 to end (mg/hour)	0.55 (0.07)	0.16 (0.03)	<0.0001
Ramsay Sedation Score AUC during drug administration	3.1 (0.04)	3.4 (0.04)	<0.0001
Ratio of Ramsay Sedation Score of 1 during drug administration (%)	7 (0.7)	4 (0.5)	0.0008

*SEM = Standard Error of Mean

As noted by Dr. Ma in his review, the Ramsay Sedation Score itself (AUC) was not a useful endpoint to consider as, for both groups, dose titration and rescue medication were used to maintain the patients at a specified level of sedation indicated by the Ramsay Score. However, a smaller ratio of Ramsay score of 1, for any particular patient, might indicate less anxiety during the treatment period. Statistically significant center effects were noted for most secondary endpoints indicating that patients in different countries either required and/or were administered differing amounts of sedative and analgesic medications.

The following additional secondary endpoints were discussed by Dr. Cortinovis in his review:

Time to extubation and weaning duration:

No statistically significant differences were noted in time to readiness for extubation or actual extubation, when that time was measured either from ICU arrival or start of study drug. No statistically significant differences were found between the treatment groups for median duration of weaning.

Nurses' and patients' assessment

Dexmedetomidine treated patients had a statistically significantly lower patient management index [defined on page 52 of Dr. Cortinovis' review] score compared with

placebo treated patients. However, the actual numerical differences were not likely to be clinically relevant, according to Dr. Cortinovis.

Patient satisfaction survey

The dexmedetomidine treated and placebo patients rated similarly their present experience with sedation compared to prior experiences, their comfort during the ICU sedation, their remembrance of pain, discomfort from breathing tube, people and noise, and whether or not they would have the same sedative treatment in the future. However, 70% of dexmedetomidine treated patients compared to 60% of placebo patients rated their overall experience as "better than expected."

Subgroup Analyses of Efficacy:

Dr. Ma has reviewed the sponsor's subgroup analyses and reports a few exceptions to the overall findings of significant efficacy of dexmedetomidine. These include:

1. Of the 43 patients in both groups at the five German centers in Study 245, only 1 (5%) in the treated group required 0 mg of midazolam during the intubation period. At the other centers more than 50% of the treated patients required no midazolam.
2. For the 20 patients at the single Austrian center in Studies 245 and 246, similar amounts of midazolam and propofol were required by the placebo and dexmedetomidine treated groups.
3. When analyzed by type of surgery, similar amounts of midazolam were required by the 34 patients undergoing head and neck surgery in Study 245 (p=0.96). Statistically significant differences were found for the two treatment groups for patients undergoing cardiac surgery, laparotomy and other surgeries in that study and all types of surgery in Study 246. However, the p-value for head and neck surgery for Study 246 was 0.052.

SAFETY:

The original NDA submission excluded the [redacted] ata from the ISS database. This fact was discovered by Dr. Cortinovis after the submission had been filed. In a teleconference in late May of 1999, the sponsor claimed that they had not included this data because it came from studies performed to assess different indications than the one that is the subject of this application. The sponsor was informed that it would be necessary for them to compile, analyze and submit this missing data. The sponsor informed us that it would take a minimum of two months to complete the assignment and an early August submission was agreed upon. The new data was submitted on August 16, 1999. This submission was found to be incomplete, with missing case report forms [CRF's], CRF's from the [redacted] which had not been translated, and missing

case report form tabulations. During a follow-up teleconference, the sponsor acknowledged the missing data and stated that they had determined some of the data to be not useful due to unavailability of CRF's or the omission of data from CRF's . They were told to immediately provide as much of the data as possible and written explanations for any data which would not be submitted. These final portions of the safety database have been submitted piecemeal since that time. In her first addendum to the medical review, Dr. Hartwell has evaluated this late data in full and carefully delineates the various parts, based on GCP suitability, availability of primary documentation, and overall importance to the safety profile of dexmedetomidine.

In an attempt to incorporate the recently submitted data into the exposure database, Dr. Hartwell created two tables [see pages 5 and 6 of her first addendum] which summarize the number of studies and the number of patients included in the supplemental ISS, broken down by GCP suitability and by those with available CRF's. She then incorporated the patients from the supplemental submissions into a table [page 6 of her first addendum] of all exposed patients, updating Dr. Cortinovis' Table 32 [page 57 of his review]. At this time, based on the information available from the sponsor, it appears that a total of 3338 subjects have been exposed to dexmedetomidine in clinical studies. However, the sponsor has categorized 11 Phase I studies (109 subjects) and 4 Phase II/III studies (146 subjects) as containing inadequate information; and this data was not included in the supplemental ISS. Thus, the overall ISS database includes 3083 subjects exposed to dexmedetomidine.

Extent of exposure by dose is summarized in the table below, based on Dr. Cortinovis' Tables 7 and 22 [pages 24 and 47, respectively, of his review] and Dr. Hartwell's Tables 4 and 5 [page 7 of her first addendum]:

Table 9.

	Continuous Infusion	Rapid Infusion	IM Administration
Phase I Studies:			
Mean Total Dose			
N	174	184	36
(µg/kg) ± SD	3.52 ± 3.97	0.90 ± 0.63	3.86 ± 3.33
Mean Total Duration			
N	174	167	10
(hr) ± SD	7.65 ± 8.26	0.13 ± 0.05	0.02 ± 0.00
Minimum	0.72	0.02	0.02
Maximum	24.02	0.18	0.02
Phase II Studies:			
Mean Total Dose			
N	1518	267	662
(µg/kg) ± SD	4.29 ± 3.09	1.00 ± 0.67	1.91 ± 0.75
Mean Total Duration			
N	1475	106	
(hr) ± SD	10.10 ± 6.54	0.05 ± 0.03	N/A
Minimum	0.02	0.02	
Maximum	39.58	0.17	
Phase III Study 245:			
Mean Total Dose			
N	178	N/A	N/A
(µg/kg) ± SD	7.0 ± 2.95		
Mean Total Duration			
N	16.6 ± 5.0	N/A	N/A
(hr) ± SD			
Phase III Study 246:			
Mean Total Dose			
N	203	N/A	N/A
(µg/kg) ± SD	7.1 ± 2.81		
Mean Total Duration			
N	14.7 ± 4.51	N/A	N/A
(hr) ± SD			

N.B. The total N for all patient/subject listings in this table does not equal the total N for the safety database. The total N here falls between the total N for patients exposed and the total N for patients in the database (those with adequate and available data), based on availability of dose and duration information from the different study sites.

During her review of the safety data, Dr. Hartwell requested more specific information on exposure by dose and duration from the sponsor. Dose by duration exposure data for all treated patients in the Phase II/III continuous infusion studies is summarized in Dr. Hartwell's Table 1 from page 2 of her second addendum:

Table 10. Extent of Exposure – Frequency of Duration by Dose
Phase II/III Continuous Infusion Studies – All-Treated Patients

Duration (hrs)	Dose (mcg/kg)									
	0-2	*>2-4*	*>4-6*	*>6-8*	*>8-10*	*>10-12*	*>12-14*	*>14-16*	*>16-18*	***Total***
0-2	151	12	1	0	0	0	0	0	0	164
>2-4	92	41	1	1	0	0	0	0	0	135
>4-6	57	195	1	0	0	0	0	0	0	253
>6-8	24	41	5	0	0	0	0	0	0	70
>8-10	24	35	17	0	0	0	0	0	0	76
>10-12	0	66	94	29	9	0	0	0	0	198
>12-14	0	32	62	55	33	5	0	0	0	187
>14-16	0	28	30	36	5	9	1	0	0	109
>16-18	1	19	27	32	10	4	5	0	0	98
>18-20	0	5	15	20	11	14	4	0	0	69
>20-22	1	1	9	13	5	1	2	4	0	36
>22-24	0	1	5	12	7	14	11	9	7	66
>24-26	0	1	0	3	2	0	2	0	0	8
>26-28	0	0	0	0	1	0	0	0	0	1
>28-30	0	0	0	0	1	0	0	0	0	1
>30-40	0	0	1	1	0	0	0	0	0	2
Total	350	477	268	202	84	47	25	13	7	1473

From Sponsor's Table of Duration by Dose, Supplement to NDA, 10-27-99, Exhibit 4
N.B. The total N corresponds to the total number of patients with available total duration data as in my Table 9, above. However, there was a discrepancy in the total N between the sponsor's ISS Supplement (submitted August 16, 1999), Appendix C, Table 2.1.2, p. 68 and Supplemental Information submitted on October 27, 1999 (p. 7). This discrepancy of 2 patients appears to be a simple error in addition.

Dose by duration exposure data for all treated patients in the Phase I continuous infusion studies is summarized in Dr. Hartwell's Table 1 from page 1 of her second addendum:

Table 11. Extent of Exposure – Frequency of Duration by Dose
Phase I Continuous Infusion Studies – All-Treated Patients

Duration (hrs)	Dose (mcg/kg)							
	0-2	*>2-4*	*>4-6*	*>6-8*	*>8-10*	*>10-12*	*>12*	Total
0-2	66	7	0	0	0	0	0	73
>2-4	13	3	1	3	0	2	0	22
>4-6	0	7	0	0	0	0	2	9
>6-8	0	10	0	0	0	0	0	10
>8-10	1	7	0	0	0	0	0	8
>10-12	0	4	5	1	0	0	0	10
>12-14	0	3	3	0	0	0	0	6
>18-20	0	1	3	0	0	0	0	4
>20-22	0	0	12	0	0	0	0	12
>22-24	0	0	7	0	6	0	6	19
>24	0	0	1	0	0	0	0	1
Total	80	42	32	4	6	2	8	174

From Sponsor's Table of Duration by Dose, Supplement to NDA, 10-27-99, Exhibit 1
N.B. The total N corresponds to the total number of patients with available total duration data as in my Table 9, above.

Deaths:

Amongst the 3083 dexmedetomidine treated patients, there were 12 deaths in the Abbott sponsored clinical studies and 1 death in [redacted] reported to the

original NDA [total deaths equals 16 with the additional deaths reported during the review period; see below]. In all of the studies combined, there were 8 deaths in the placebo groups (N = 1495) and none in the comparator groups (N = 407) reported to the original NDA.

Dr. Cortinovis has summarized the 12 Abbott deaths in his review and Dr. Hartwell has summarized [redacted] in her addendum. While there were no deaths that could clearly be attributed directly to dexmedetomidine, a few of the cases raise concerns regarding intraoperative or postoperative cardiovascular events which may have, ultimately, contributed to the patients' deaths.

> Patient 1115, Study 95-002, was an elderly male who underwent a low anterior colon resection. The patient experienced intermittent hypotension and the dexmedetomidine infusion was discontinued after only two hours. The patient experienced a cardiac arrest two days later. An autopsy did document severe atherosclerotic cardiac disease. Dr. Cortinovis assessed this case as unrelated to study drug. However, if the episodic hypotension was exacerbated by the dexmedetomidine infusion, it is possible that significant damage was done to the myocardium, allowing an already diseased organ system to deteriorate and fail over the next two days.

> Patient 0622, Study 95-004, was a 59 year old male who underwent coronary artery bypass surgery and developed acute renal failure postoperatively. Dr. Cortinovis determined this case to be unrelated to study drug. The exact postoperative course leading to death is not clear, but the renal failure could certainly have been directly or indirectly related to dexmedetomidine, a drug with an established adverse event profile that includes hypotension. However, it is important to note that the patient's preoperative medical problems included hypertension, hypercholesterolemia, paroxysmal atrial fibrillation, and chronic renal insufficiency.

> Patient 10202, Study W97-246, was a 74 year old male who underwent coronary artery bypass surgery and developed hypotension postoperatively, soon after the dexmedetomidine infusion was started. Episodes of hypotension continued and the study drug was discontinued 9 hours after initiation. The patient then developed renal insufficiency, but was reportedly stable over the next 3 days. He then suffered an acute myocardial infarction and died. Dr. Cortinovis assessed the relationship of study drug to this patient's death to be "doubtful." Again, the postoperative hypotension may have been a complication of, or have been complicated by, the dexmedetomidine infusion. Over time, this may have resulted in a deterioration in cardiac function and contributed to the patient's terminal events.

Patient 109, Study 97-249, was 47 year old who underwent coronary bypass surgery. Approximately 14 hours following initiation of the dexmedetomidine infusion, the patient developed circulatory collapse, hypotension and an acute myocardial infarction. The infusion was discontinued and the patient returned to the operating room for repair of an incomplete coronary revascularization. The patient died of mutiorgan failure following that procedure. Dr. Cortinovis determined that the proximate cause of death is not clear, but "...is of the opinion that the cause of death was the direct result of the surgical repair." [page 63 of his review] As with the above cases, this patient's postoperative cardiovascular collapse may have been directly or indirectly related to the dexmedetomidine infusion.

Patient 211, Study 3005006, was a 73 year old male who underwent coronary artery bypass surgery and received infusions of dexmedetomidine both intraoperatively and postoperatively. His postoperative course was complicated by hyperglycemia, acidosis, hemodynamic instability, and decreased urine output. Following extubation he became agitated and confused, requiring sedation and supplemental oxygen to maintain his saturation. Three days after surgery the patient's intravenous line became disconnected and he died of massive blood loss. The investigators concluded that the death was not due to study drug. Dr. Hartwell states that "...if dexmedetomidine was a contributor or initiator of the patient's confusional state and if the patient's ongoing confusion and agitation was the cause of an inadvertent intravenous disconnection, the study agent must be secondarily implicated in this patient's death. From the data provided, it is not possible to completely discount dexmedetomidine as a factor in the initial agitation/confusion episode." [page 9 of her addendum] As Dr. Hartwell notes, the patient's change in mental status may have been due to multiple factors. Certainly, the documented hemodynamic instability and decreased urine output may both have been the result of dexmedetomidine induced hypotension and hypoperfusion, and have resulted in hypoxic-ischemic encephalopathy.

At Dr. Hartwell's request, the sponsor provided information on two additional deaths reported with minimal information in the 120-Day Safety Update from ongoing, blinded Phase II studies.

Patient 104, Study W98-263, was a 79 year old female with multiple medical problems was treated with a continuous infusion of dexmedetomidine in the ICU following myocardial infarction and cardiac arrest and resuscitation. During treatment she experienced recurrent hypotension and bradycardia. All treatments were discontinued after 18 hours and the patient died of multiorgan failure. Dr. Hartwell's conclusion

that the sponsor cannot rule out that study drug contributed to the patient's demise is appropriate.

Patient 101, Study W98-264, was a 58 year old male with multiple medical problems treated with a continuous infusion of dexmedetomidine in the ICU. The patient experienced two episodes of transient hypotension which responded readily to reduction in the dexmedetomidine infusion rate. The patient received dexmedetomidine for a total of 50 hours, at which time all supportive care was withdrawn. The patient died of multiorgan failure soon after. Once again, Dr. Hartwell's conclusion that the sponsor cannot rule out that study drug contributed to the patient's demise is appropriate.

Dr. Hartwell next compared data on deaths submitted to the sponsor's IND for dexmedetomidine, [redacted] [Annual Report dated 3-24-99] and that submitted to the original NDA and the Safety Update. Nine deaths not reported to the NDA or Safety Update were documented in the Annual Report. One death occurred in a patient exposed to dexmedetomidine, 3 in placebo treated patients, and five in patients without documentation of treatment group. Clarification of this data was requested of the sponsor in September 1999 and received on October 1, 1999. In that communication, the sponsor explains that serious adverse events [SAE's], presumably incorporating deaths, occurring greater than 24 hours after discontinuation of treatment were included in a special company database, but not necessarily in the NDA database.

Clarification of the discrepancies was requested of the sponsor. On pages 6 and 7 of her second addendum, Dr. Hartwell summarizes the information received from the sponsor. Only 1 of the patients in this group of deaths was exposed to dexmedetomidine.

Patient 11601, Study 97-246, was a 73 year old male who underwent pneumonectomy for lung cancer. He received a continuous infusion of dexmedetomidine for 7 hours at constantly decreasing doses. His course was complicated by severe hypotension requiring treatment with dopamine, followed by cardiac arrest from which the patients was resuscitated. He died five days later. The investigator attributed the death to "poor cardiac function – myocardial hypersensitivity to dopamine", and determined it to be "unrelated" to study drug. As per Dr. Hartwell's discussion, it remains possible that dexmedetomidine exposure contributed to the patient's death.

Discontinuations:

Dr. Cortinovis has summarized the narratives of all 41 patients who discontinued due to adverse events in his review. No clearcut trends or conclusions may be drawn from those summaries.

My review of the sponsor's Table 2.1.5.11, "Summary of Discontinuation Due to Adverse Events; All Treated Patients in Phase II/III Continuous Infusion Studies", pages 166-168, Volume 1.302, revealed no events resulting in patient discontinuation that occurred with a frequency greater than 1%. In particular, circulatory failure, hypotension, cardiac arrhythmias, myocardial infarction and hypoxia each occurred in less than 1% of both dexmedetomidine treated and placebo patients. My review of the sponsor's Table 2.2.5.11, "Summary of Discontinuation Due to Adverse Events; All Treated Patients in Phase II/III Continuous Infusion ICU Sedation Studies", pages 275-277, Volume 1.303, revealed similar findings.

In the 120-Day Safety Update, the sponsor reported on 1 treated subject who discontinued due to an adverse event. That subject suffered a seizure after receiving study drug and discussed below under Serious Adverse Events.

It is worth noting here that there are discrepancies in the numbers of patients listed as discontinuations in the sponsor's initial ISS documents and the follow-up documents. There are also discrepancies internally within the original ISS. However, with all available data regarding this patient subset having been reviewed by either Dr. Cortinovis, Dr. Hartwell, or myself, there is no evidence that the adverse event profile was unusual or unexpected. Thus, it is unlikely that a full accounting of discontinued patients would provide new information that would significantly affect our decision regarding approvability.

Serious Adverse Events:

Dr. Cortinovis' review of SAE's consisted of copies of modified sponsor's tables which summarized the incidence of all SAE's in all clinical trials. Thereforee, I requested that Dr. Hartwell undertake a more thorough analysis of this data.

In her first addendum, Dr. Hartwell reports that 5 subjects in the Phase I trials experienced SAE's. The events that Dr. Hartwell concludes are possibly related to study drug exposure are sinus arrest (2), bradycardia, hypotension, convulsions, and allergic reaction after transdermal application.

In the Phase II/III trials, Dr. Hartwell reports that 9% of patients in the Abbott sponsored continuous infusion studies and 11% of patients in the non-Abbott sponsored continuous infusion studies experienced SAE's. The overall incidence was similar to the randomized placebo population for these studies (9% and 10%, respectively). In the Abbott continuous infusion studies, the only SAE's occurring more frequently in the dexmedetomidine treated patients compared to the placebo treated patients were: hypotension (4% vs. 2%), hypertension (2% vs. 1%), and bradycardia (2% vs. 0%). All other SAE's occurred in less than 1% of dexmedetomidine treated patients. Similar data is unavailable for the non-Abbott studies.

As summarized in Dr. Hartwell's Table 3, page 4 of her second addendum, the incidences of the treatment emergent SAE's myocardial infarction and cardiac arrest were less than 1% in both the dexmedetomidine treated and placebo treated patients. In her Table 4 on page 4 of the addendum, Dr. Hartwell summarizes the treatment emergent respiratory adverse events in the Phase II/III continuous infusion studies. The incidences of all events were similar between the dexmedetomidine and the placebo treated patients.

In her first addendum, Dr. Hartwell summarizes the SAE's reported to the 120-Day Safety Update. Most of these events appeared to be unrelated to study drug exposure. Three patients [two of whom have already been discussed in the section of Deaths] experienced hemodynamic instability which might have been directly or indirectly related to dexmedetomidine exposure. One subject in a Phase I study experienced a single seizure after receiving an infusion of 1.25 ng/mL dexmedetomidine for approximately 18.5 hours. Although he had no history of seizure disorder, he did have a history of head trauma. Nevertheless, the dexmedetomidine may have directly or indirectly contributed to this event. Dr. Hartwell concludes that the overall incidence of SAE's in the 120-Day Safety Update is consistent with what has been reported in the original and in the supplementary NDA submissions.

Once again, as with the reporting of Deaths, the sponsor explained that SAE's reportedly occurring greater than 24 hours after discontinuation of treatment were included in a special company database, but not necessarily in the NDA database. Consequently, as Dr. Hartwell notes on page 5 of the second addendum: "...inaccuracies in both the identification of serious adverse events and the total number of events reported for each study are a possibility."

Other Adverse Events:

Dr. Cortinovis' Table 42, page 99 of his review [reproduced below], summarizes the incidence and dose association of the most common adverse events seen in the Phase I continuous infusion studies. Dry mouth and somnolence were extremely common in some target concentration groups (up to 73% and 85%, respectively), with some non-dose relatedness possibly explained by incomplete reporting.

Table 12. Most Common[a] Treatment Emergent Adverse Events By Target Dexmedetomidine Plasma Concentration: All Dexmedetomidine Treated Subjects Phase I Continuous Infusion Studies

	Target Dexmedetomidine Plasma Concentration (ng/mL)					
Adverse Event[b]	0.1-0.2 (N=25)	0.3 (N=59)	0.4-0.5 (N=34)	0.6 (N=61)	1.25 (N=12)	Increasing Dex Conc (N=22)
Subjects with at least one treatment-emergent adverse event	24(96%)	39(66%)	27(79%)	39(64%)	12(100%)	10(45%)
Mouth dry	5(20%)	16(27%)	9(26%)	12(20%)	9(75%)	1(5%)
Somnolence	17(68%)	10(17%)	20(59%)	8(13%)	10(83%)	0
Headache	2(8%))	15 (25%)	5(15%)	11(18%)	4(33%)	2 (9%)
Hypotension	14(56%)	9(15%)	16(47%)	9(15%)	0	1(5%)
Nausea	1(4%)	9(15%)	2(6%)	2(3%)	0	5 (23%)
Hypoxia	0	1(2%)	0	1(2%)	0	0
Dizziness	3 (12%)	3 (5%)	1(3%)	1(2%)	1(8%)	2(9%)
Bradycardia	1(4%)	4(7%)	0	3 (5%)	1(8%)	4(18%)
Muscle contractions involuntary	0	3 (5%)	1(3%)	5 (8%)	0	2(9%)
Pallor	0	8(14%)	0	5(8%)	0	0
Apnea	0	4(7%)	0	4(7%)	0	0
Stupor	1(4%)	3 (5%)	2(6%)	1(2%)	1(8%)	1(5%)
Hyperkinesia	0	3 (5%)	1(3%)	5 (8%)	0	0
Pain	0	4(7%)	1(3%)	2(3%)	0	1(5%)
Pharyngitis	1(4%)	4(7%)	1(3%)	4(7%)	0	0
Paresthesia	0	0	0	4(7%)	1(8%)	0
Xerophthalmia	1(4%)	5 (8%)	3 (9%)	0	0	0
Fatigue	0	3 (5%)	0	3 (5%)	1(8%)	0
Hallucination	0	0	0	3 (5%)	4 (33%)	0
Vomiting	0	5(8%)	0	0	0	0
Agitation	2(8%)	0	4(12%)	0	0	1(5%)
Pruritus	1(4%)	4(7%)	1(3%)	1(2%)	0	0
Rhinitis	1(4%)	2 (3%)	1(3%)	0	1(8%)	0
Back pain	1(4%)	2 (3%)	0	0	1(8%)	1(5%)
Vision abnormal	0	4(7%)	0	2 (3%)	0	0
Abdominal pain	0	1(2%)	2(6%)	1(2%)	0	1(5%)
Conjunctivitis	0	0	0	1(2%)	3 (25%)	1(5%)

Sponsor's Table 43, ISS Vol. 8/10-239-135

a: Experienced by≥2% of all dexmedetomidine-treated subjects in the Phase I studies.

b: Subjects may have been counted in more than one column if they received treatment in more than one treatment period, but a subject was counted only once in a given column.

Dex = Dexmedetomidine Concs = concentrations

The most common adverse events occurring in the Phase II/III continuous infusion studies are summarized in Dr. Cortinovis' Table 43 [page 100 of his review], reproduced below:

Table 13. Most Common* Treatment Emergent Adverse Events by Total Dose of Dexmedetomidine: All Treated Patients in Phase II/III Continuous Infusion Studies

	Total Dexmedetomidine Dose (mcg/kg)					
Adverse Event	0-1 (N=88)	>1 - 3 (N=455)	>3 - 5 (N=300)	>5 -7 (N=226)	>7 - 10 (N=173)	>10 (N=92)
Patients with at least one treatment-emergent adverse event	66(75%)	255 (56%)	183 (61%)	147(65%)	104(60%)	56(61%)
Hypotension	29(33%)	145(32%)	92(31%)	65(29%)	36(21%)	25 (27%)
Hypertension	5(6%)	47(10%)	39(13%)	45(20%)	28(16%)	12(13%)
Nausea	24(27%)	53 (12%)	38(13%)	28(12%)	14(8%)	5 (5%)
Bradycardia	8(9%)	28(6%)	21(7%)	12(5%)	15(9%)	10(11%)
Tachycardia	4(5%)	25 (5%)	12(4%)	14(6%)	4(2%)	5 (5%)
Fever	3 (3%)	20(4%)	15(5%)	9(4%)	10(6%)	4(4%)
Hypoxia	19(22%)	14(3%)	9(3%)	8(4%)	4(2%)	4(4%)
Anemia	1 (1%)	15(3%)	17(6%)	14(6%)	4(2%)	1 (1%)
Vomiting	2(2%)	14(3%)	12(4%)	11(5%)	6(3%)	3 (3%)
Hemorrhage NOS	2(2%)	13 (3%)	9(3%)	4(2%)	5 (3%)	3 (3%)
Pain	5 (6%)	10(2%)	7(2%)	7(3%)	4(2%)	1 (1%)
Rigors	0	13 (3%)	8(3%)	5(2%)	4(2%)	3 (3%)
Atrial fibrillation	0	10(2%)	9(3%)	6(3%)	6(3%)	2(2%)
Mouth dry	0	3 (<1%)	4(1%)	6(3%)	11(6%)	6(7%)
Agitation	1 (1%)	9(2%)	9(3%)	3 (1%)	4(2%)	4(4%)

Sponsor's Table 44 ISS Vol. 8/10-239-137

NOS = not otherwise specified

*: Experienced by ≥2% of all Dexmedetomidine treated patients in Phase II/III continuous infusion studies

No apparent dose relationship can be seen for these adverse events, except for dry mouth. The high incidence of hypoxia in the 0-1 μg/kg group is attributable to a single study [dexmedetomidine-96-012] in which hypoxia was reported by ≥ 75% of patients in all treatment groups, including the placebo group.

A comparison of the adverse events occurring in the Phase II/III continuous infusion studies between the dexmedetomidine treated and placebo treated patients can be seen in the table below:

Table 14. Events Experienced by ≥ 2% of All Dexmedetomidine Treated Patients in Phase II/III Continuous Infusion ICU Sedation Studies

Adverse Event	Randomized Dexmedetomidine		
	Dexmedetomidine Only (N = 158)	Dexmedetomidine and Midazolam (N = 104)	Dexmedetomidine and Propofol (N = 125)
Patients with at least one treatment-emergent adverse event:	100 (63%)	79 (76%)	80 (64%)
Hypotension	47 (30%)	25 (24%)	36 (29%)
Hypertension	23 (15%)	25 (24%)	15 (12%)
Nausea	11 (7%)	15 (14%)	16 (13%)
Bradycardia	8 (5%)	5 (5%)	14 (11%)
Dry Mouth	4 (3%)	3 (3%)	6 (5%)
Fever	1 (<1%)	11 (11%)	6 (5%)
Vomiting	5 (3%)	3 (3%)	8 (6%)
Atrial Fibrillation	11 (7%)	5 (5%)	0
Hypoxia	6 (4%)	5 (5%)	5 (4%)
Anemia	4 (3%)	4 (4%)	3 (2%)
Pain	6 (4%)	1 (<1%)	2 (2%)
Tachycardia	2 (1%)	6 (6%)	4 (3%)
Hemorrhage	5 (3%)	5 (5%)	2 (2%)
Pleural Effusion	1 (<1%)	5 (5%)	2 (2%)
Hypovolemia	0	3 (3%)	2 (2%)
Thirst	3 (2%)	2 (2%)	3 (2%)
Rigors	2 (1%)	5 (5%)	1 (<1%)
Hyperpyrexia	3 (2%)	3 (3%)	1 (<1%)
Agitation	1 (<1%)	5 (5%)	2 (2%)
Somnolence	4 (3%)	0	0
Atelectasis	3 (2%)	1 (<1%)	1 (<1%)
Oliguria	2 (1%)	4 (4%)	0

Adverse Event	Placebo		
	Placebo Only (N = 71)	Placebo and Midazolam (N = 150)	Placebo and Propofol (N = 158)
Patients with at least one treatment-emergent adverse event:	46 (65%)	104 (69%)	88 (56%)
Hypotension	10 (14%)	24 (16%)	14 (9%)
Hypertension	6 (8%)	23 (15%)	39 (25%)
Nausea	6 (8%)	12 (8%)	18 (11%)
Bradycardia	4 (6%)	4 (3%)	2 (1%)
Dry Mouth	1 (1%)	2 (1%)	1 (<1%)
Fever	2 (3%)	9 (6%)	6 (4%)
Vomiting	3 (4%)	9 (6%)	9 (6%)
Atrial Fibrillation	2 (3%)	7 (5%)	4 (3%)
Hypoxia	3 (4%)	8 (5%)	3 (2%)
Anemia	0	7 (5%)	2 (1%)
Pain	1 (1%)	5 (3%)	1 (<1%)
Tachycardia	1 (1%)	11 (7%)	6 (4%)
Hemorrhage	2 (3%)	9 (6%)	6 (4%)
Pleural Effusion	1 (1%)	0	3 (2%)
Hypovolemia	2 (3%)	5 (3%)	3 (2%)
Thirst	0	1 (<1%)	0
Rigors	1 (1%)	4 (3%)	8 (5%)
Hyperpyrexia	2 (3%)	6 (4%)	2 (1%)
Agitation	2 (3%)	5 (3%)	4 (3%)
Somnolence	2 (3%)	2 (1%)	2 (1%)
Atelectasis	4 (6%)	2 (1%)	7 (4%)
Oliguria	0	2 (1%)	1 (<1%)

Modified sponsor's Table 48, ISS Vol. 8/10-239-143

As noted by Dr. Cortinovis on page 102 of his review, there was an increased incidence of both hypotension and hypertension in the dexmedetomidine treated patients compared to any of the placebo groups. Patients in the dexmedetomidine/propofol group had a higher incidence of bradycardia compared with patients in the other groups. The sponsor has speculated that dexmedetomidine may exacerbate the bradycardia known to occur with propofol.

Dr. Cortinovis includes in his review discussion of the adverse event profile for different age categories, by gender, by disease (specifically renal and hepatic impairment), and by type of surgical procedure that the patient underwent. The only clinically significant result of these analyses is the finding of an increased incidence of hypertension, fever, tachycardia, rigors, agitation and atelectasis in patients who underwent head and neck surgery compared to patients who underwent cardiac surgery, laparotomy, or "other" surgery [see Dr. Cortinovis' Table 47, page 106 of his review]. This occurred in both the dexmedetomidine treated and the placebo treated patients, though with a slightly lower incidence in the latter group. This finding may be explained by the fact that many of the patients undergoing head and neck surgery would have been cancer victims with compromised immune systems and a resultant increased incidence of infection. In fact, when reviewed by Dr. Hartwell, 100% of the patients in W97-246 underwent surgery for cancer related complications.

Laboratory Values:

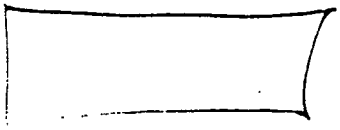
Although statistically significant differences were noted between the dexmedetomidine treated and placebo treated patients in the mean change from baseline for hematocrit, hemoglobin, red blood cells , and serum glucose level, these changes were not clinically significant. Dr. Cortinovis' Table 41, page 95 of his review, summarizes the laboratory data and these specific findings.

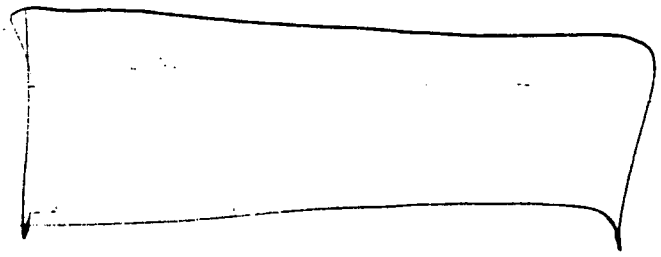
Vital Signs:

The vital sign data presented in the ISS was from the Phase II/III ICU sedation studies only (N = 576). This was explained to be due to failure of a novel monitoring system used in the other studies to provide accurate data.

Although there was a statistically significantly greater degree of hypotension in the dexmedetomidine treated patients compared to the placebo patients, this difference was not clinically significant. Bradycardia also occurred significantly more frequently in the dexmedetomidine group. The mean heart rate appeared to be approximately 10 bpm slower for those patients compared to the placebo patients, though still within a clinically acceptable range. Small, statistically, but not clinically significant differences in central venous pressure were found between the groups; with the dexmedetomidine group having the lower values.

CHEMISTRY, MANUFACTURING AND CONTROLS:





PHARMACOLOGY AND TOXICOLOGY:

Dr. Geyer found no animal toxicity that would raise concerns regarding the approvability of this product. However, long term continuous intravenous administration is only now being studied, at our request. After subcutaneous infusion of 10 µg/kg/hr dexmedetomidine to dogs for one week, the cortisol response to ACTH stimulation was diminished by about 40%. In light of the clinical findings of adrenal suppression in patients treated with the related compound etomidate, further investigation during long term administration may be warranted.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS:

Dr. Doddapaneni notes that the pharmacokinetics of dexmedetomidine were affected by hepatic impairment. The mean clearance values for subjects with mild, moderate and severe hepatic impairment were 74%, 64% and 53%, respectively, of those observed in normal healthy subjects. Dosage adjustment for patients with hepatic impairment is recommended.

ABUSE LIABILITY:

Dr. Hayes has recommended that dexmedetomidine not be scheduled under the Controlled Substances Act as there is a lack of evidence to support such a regulatory action. However, if other dosage forms of dexmedetomidine are approved, the abuse liability of those new formulations would have to be reassessed.

Careful postmarketing surveillance for evidence of trafficking of the drug out of the hospital environment and for community abuse and dependence problems will be necessary for this sedative product.

COMMENTS:

The sponsor has provided evidence of effectiveness from two adequate and well-controlled trials for dexmedetomidine when administered as a continuous intravenous infusion for postoperative sedation over a 24 hour period. On subgroup analysis, there was a suggestion that dexmedetomidine may be less effective in patient's undergoing head and neck surgery compared to other types of major surgery. Of interest, this same group of patients, all suffering from significant malignancies, appeared to have an adverse event profile suggestive of infection.

While there appears to be evidence of some analgesic effect from treatment with dexmedetomidine, the studies were not designed to assess whether this is intrinsic analgesic activity or potentiation of morphine induced analgesia. The measures used to assess the anxiolytic activity of dexmedetomidine were not adequate to determine whether a patient was anxious or not anxious, in light of the fact that patients can appear calm while experiencing dysphoria. Finally, the measures used to assess patient manageability have not been validated for this use. In addition, the so-called "Patient Management Index" was not prospectively defined and while the difference between the placebo and dexmedetomidine groups was statistically significant, these differences were not clinically significant.

The safety profile of this new molecular entity is as expected for an α-2-adrenoreceptor agonist with clinically significant hypotension and bradycardia being the most prominent adverse events. Concerns regarding the effect of long-term continuous infusion of dexmedetomidine on the adrenal-pituitary axis will require further investigation. There is currently no information on the use of this product in pediatric subjects or patients.

RECOMMENDATIONS:

I recommend that this application be approved with appropriate labeling. In addition, Phase IV commitments from the sponsor to perform studies to evaluate pediatric pharmacokinetics and clinical use, as well as preclinical and clinical safety evaluations of adrenal suppression, should be required. Prior to recommending administration of dexmedetomidine for greater than 24 hours, the sponsor should also undertake appropriate studies to assure persistent effectiveness and that there are no new safety concerns that arise when the drug is administered as a long-term continuous infusion.

/S/

Bob A. Rappaport, M.D.

November 5, 1999

November 5, 1999

Cc: Original NDA 21-038
HFD-170: Division File
HFD-170:
McCormick
Rappaport
Hartwell
Ma
Doddapaneni
Geyer
Theodorakis
Hayes
Samanta

APPEARS THIS WAY ON ORIGINAL

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS

Brand Name:	[redacted]
Generic Name:	Dexmedetomidine HCl
Indication:	Sedation for Intensive Care
NDA Classification:	1S
NDA Number:	21-038
Original Receipt Date:	18 December 1998
Clinical Reviewer:	Charles R. Cortinovis, MD MPH
Review Completed:	24 August 1999

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