

## Study Design

This was a phase I, single center, open-label study. After stable anesthesia was achieved using alfentanil and propofol, rocuronium administration began at an initial infusion rate of 200 µg/kg/hour (note: recommended initial infusion rate for continuous infusion is 600 to 720 µg/kg/hour). It was then adjusted to maintain a stable T1 at 50% of the baseline value. After stabilization of neuromuscular block, dexmedetomidine was administered to achieve a steady concentration of 0.6 ng/mL using a computer controlled infusion pump. After 45 minutes of dexmedetomidine infusion, all infusions were stopped.

## Results and Discussion

Statistical analysis was done to compare rocuronium concentrations prior to and 15, 30, and 45 minutes after initiation of dexmedetomidine infusion by a paired t-test. No statistically significant difference was found between the rocuronium concentrations immediately before the start of dexmedetomidine infusion and concentrations 15 and 30 minutes later. However, there was a significant difference for the comparison of pre-dexmedetomidine rocuronium concentrations and those 45 minutes later. It should be noted that the elapsed time from last change in rocuronium infusion rate until dexmedetomidine infusion began ranged from 10-24 minutes meaning that rocuronium with a terminal half-life of 71 minutes will not achieve new steady state concentrations within the 45 minutes of dexmedetomidine infusion. This is reflected in the small rise in rocuronium concentrations during the 45 minutes of dexmedetomidine infusion. The small but statistically significant difference between concentrations of rocuronium prior to dexmedetomidine infusion as compared to 45 minutes after the start of dexmedetomidine may be due to rocuronium not having achieved steady-state (1.66 versus 1.79 ng/mL).

The changes in neuromuscular block before and after dexmedetomidine infusion were small (6.6% in T<sub>1</sub>%), clinically undetectable, and considered clinically unimportant by the investigator.

Table 1. Mean dexmedetomidine and rocuronium concentrations.

Time After Start of Dexmedetomidine Administration (minutes)	Dexmedetomidine Concentrations (ng/mL)	Rocuronium Concentrations (ng/mL)
0	0.002 ± 0.005	1.66 ± 0.29
15	1.03 ± 0.15	1.73 ± 0.37
30	0.96 ± 0.15	1.78 ± 0.43
45	0.94 ± 0.14	1.79 ± 0.41

Note: Lack of analytical assay validation data precludes the use of rocuronium pharmacokinetic information in the package insert.

## IN VITRO METABOLISM

**Study Type:** *In Vitro* Metabolism and inhibition.

**NDA:** 21-038    **Submission Date:** 12/18/98    **Volume:** 1.49    **Protocol:** R&D/97/757

### **Objective:**

To identify the hepatic cytochrome P450 proteins involved in the metabolism of [<sup>3</sup>H]dexmedetomidine in human liver microsomes and human B-lymphoblastoid microsomes containing cDNA expressed cytochrome P450 proteins.

### **Conclusions:**

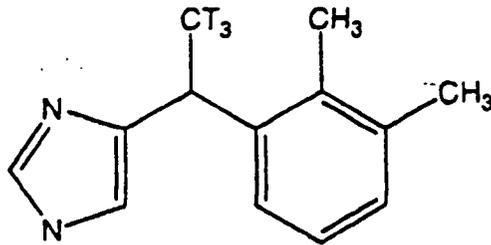
Based on the results from this study, it was concluded that the hydroxylation of dexmedetomidine to 3-hydroxy dexmedetomidine and H-3 is largely mediated by CYP2A6, although other CYP forms may also play an ancillary role. Evidence for the involvement of CYP2A6 included: 1) 8-methoxypsoralen, a CYP2A6-selective inhibitor, inhibited (41-59%) the hydroxylation to both products; 2) coumarin, a CYP2A6-selective substrate, inhibited (34%) the hydroxylation to 3-hydroxy dexmedetomidine; 3) hydroxylation was also observed with human B-lymphoblastoid microsomes containing cDNA-expressed CYP2A6; and 4) the hydroxylation of dexmedetomidine was inhibited (33%) by a CYP2A6 antibody. Inhibition by CYP2A6 selective inhibitors, including antibodies, was incomplete and may indicate the involvement of one or more other CYP isozymes in human liver microsomes. Furthermore, minimal inhibition (<20%) by selective inhibitors of CYPs other than CYP2A6, lend credence to speculation that more than one other CYP isozyme might be involved. Several other cDNA expressed CYPs were also capable of catalyzing the metabolism of dexmedetomidine to one or both major products indicating that other CYP isoforms (e.g., CYP1A2, CYP2E1, CYP2D6 and CYP2C19) may play a role in the hydroxylation of dexmedetomidine.

The dexmedetomidine IC<sub>50</sub> values for inhibition of the various isoforms ranged from 0.2-3.3 μM for the inhibition of 1A1 (2.7 μM), 1A2 (2.0 μM), 2A6 (70 μM), 2C19 (3.3 μM), 2D6 (1.3 μM), 2E1 (2.2 μM), and 3A4 (0.65 μM). Since the plasma concentrations of dexmedetomidine at clinically relevant doses are very low (≤10 ng/mL; ≤0.04 μM) compared to the *in vitro* determined IC<sub>50</sub> values, the possibility of an inhibitory effect of dexmedetomidine on the metabolism of coadministered drugs *in vivo* in humans appears to be unlikely. In a clinical interaction study, dexmedetomidine did not have any effect on the pharmacokinetics of midazolam, a CYP3A substrate. The lack of inhibitory effect is possibly due to very low plasma levels of dexmedetomidine (0.2-0.4 ng/mL) observed in this study, which are several fold lower than the *in vitro* determined IC<sub>50</sub> values for CYP3A4 inhibition (0.65 μM; 110 ng/mL).

## Experimental

### Drugs

Dexmedetomidine was labeled with tritium, as shown in the figure below:

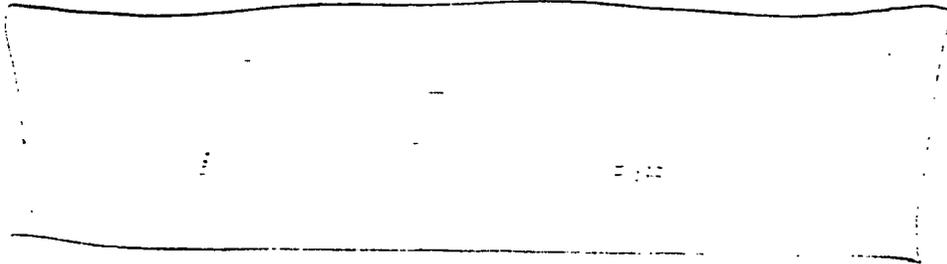


[<sup>3</sup>H]Dexmedetomidine (Lot 55585-ST-108; 66 Ci/mmol; hydrochloric acid salt) was dissolved in ethanol and stored at -20°C. The radiochemical purity was greater than 97%. Unlabeled dexmedetomidine (Lot No. 031940-002) was combined with the labeled drug only for final incubations requiring concentrations greater than 0.05 μM.

### Preparation of Liver Microsomes

Transplant quality human liver tissue was obtained from \_\_\_\_\_  
\_\_\_\_\_ was received at Abbott Laboratories within  
24 hours of removal from the donor. Based on studies with microsomes containing  
cDNA expressed CYPs and given the potential role of CYP2D6 in the oxidative  
metabolism of dexmedetomidine, liver microsomes prepared from an extensive  
metabolizer (ID:1211961; male subject) and a poor metabolizer (ID:415961; male subject)  
of CYP 2D6 substrates were used in this study.

\_\_\_\_\_ subsequently homogenized with \_\_\_\_\_ and the resultant homogenate  
was centrifuged : \_\_\_\_\_ it was carefully

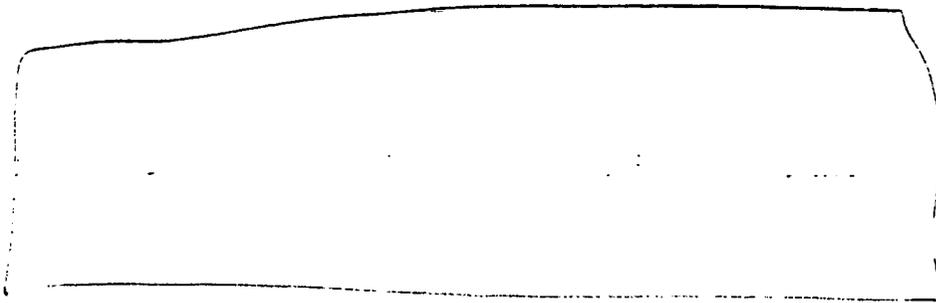


at

### ***In Vitro* Metabolism of [<sup>3</sup>H]Dexmedetomidine**

#### **Assay System**

*In vitro* incubations of [<sup>3</sup>H]dexmedetomidine with human hepatic microsomes were performed at



Involvement of the CYP system in the metabolism of both compounds was assessed by omission of the NADPH and by the use of several CYP isoform selective inhibitors.

#### **Identification of the Oxidative Metabolites of Dexmedetomidine Produced by Human Liver Microsomes**

*In vitro* incubations of [<sup>3</sup>H]dexmedetomidine with human hepatic microsomes for the



**Table 3.** IC<sub>50</sub> values for inhibition of dexmedetomidine against the different cytochrome P450 isoforms.

Cytochrome P450 isoform	Substrate	IC <sub>50</sub> (μM)
1A1	Ethoxyresorufin O-deethylase	2.7
1A2	Ethoxyresorufin O-deethylase	2.0
2A6	Coumarin 7-hydroxylase	70
2C19	S-mephenytoin 4-hydroxylase	3.3
2E1	Chlorzoxazone 7-hydroxylase	2.2
3A4	Testosterone 6β-hydroxylase	0.65
2D6	Dextromethorphan O-demethylase	1.8

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

**ABUSE LIABILITY ASSESSMENT**

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<b>NDA:</b>	21-038
<b>SPONSOR:</b>	Abbott Laboratories
<b>DRUG:</b>	_____ (Dexmedetomidine Hydrochloride)
<b>CHEMICAL NAME:</b>	(+)-4-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole
<b>DOSAGE FORM:</b>	Injectable solution (2 mL Ampul/2 mL Vials)
<b>STRENGTHS:</b>	100 mcg/mL
<b>INDICATION:</b>	ICU Sedative
<b>DATE SUBMITTED:</b>	February 4, 1999
<b>DATE Rcd. BY REVIEWER:</b>	February 10, 1999
<b>REVIEWER:</b>	BeLinda A. Hayes, Ph.D.
<b>REVIEWER DATE:</b>	July 20, 1999

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**BACKGROUND**

Abbot Laboratories has submitted NDA 21-038 for \_\_\_\_\_ (dexmedetomidine hydrochloride) to Food Drug Administration Division of Anesthetic, Critical Care, and Addiction Drug Products. \_\_\_\_\_ is indicated for ICU sedation. Dexmedetomidine, (+)-4-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole hydrochloride, is an  $\alpha_2$  adrenergic receptor agonist. It is the pharmacological active dextroisomer of medetomidine which is marketed in Scandinavian countries as a sedative/analgesic agent for veterinary use in dogs and cats under the tradename Dominator. It is an  $\alpha_2$  adrenergic receptor agonist with high potency and specificity. Its primary activities include: sedation, anesthesia, anesthetic-sparing effects, analgesia and anxiolytic activities. Its pharmacological activity is very similar to clonidine.

Per 21 CFR 314.50(5)(vii) when a NDA is submitted for new pharmaceutical product, which demonstrates similar pharmacological profile and/or structural similarity with a known drug of abuse or there are evidences of dependence producing potential, the sponsor must submit an abuse liability assessment package. This package must contain a description and analyses of studies or information related to abuse of the drug and a scheduling proposal for the drug product. \_\_\_\_\_ s these criteria. It has been demonstrated that dexmedetomidine's pharmacological action is very similar to that of clonidine. It has been documented that clonidine has been abused in patients with a history of opiate and alcohol dependencies (Dy and Yates, 1996; Lauzon, 1992; Sharma and Newton, 1995; Anderson, *et al.*, 1997); henceforth, the potential of abusing dexmedetomidine does exist. Preclinical studies have shown that dexmedetomidine has dependence potential in rats and primates, and functions as a positive reinforcer in primates. In

compliance with the requirement of 21 CFR 314.50(5)(vii), Abbott Laboratories submitted with the NDA an abuse liability assessment package. Evaluation of the compound's chemical, pharmacological (both preclinical and clinical), pharmacokinetics, and pharmacodynamic profiles of the compound, and the adverse effects associated with the compound are the basis of the abuse liability assessment and the recommendation for scheduling under the CSA.

#### ABUSE LIABILITY INFORMATION PROVIDED IN THE SUBMISSION.

The Sponsor's abuse liability data submitted in the NDA included the following:

- **Preclinical Study.** Report by K. Ando entitled "Dependence study on dexmedetomidine in rhesus monkeys and rats." Osaka, Japan. Preclinical Research Laboratories, June 1997.
- **Clinical Studies.** The sponsor did not conduct any studies to specifically address the abuse liability of dexmedetomidine. They submitted results from studies W97-028, W97-249, W97-245, and W97-246. These studies included assessment of pharmacokinetics and physiological parameters and adverse events which the sponsor felt had clinical relevance in evaluation of the potential for development of dependence.
- Published literature that the sponsor felt was pertinent to the abuse potential of dexmedetomidine.
- Information on the treatment of dexmedetomidine overdose.
- The sponsor's recommendation for scheduling dexmedetomidine under the Controlled Substances Act.

#### ABUSE POTENTIAL OF DEXMEDETOMIDINE.

**Preclinical Abuse Liability Assessment.** The abuse potential of dexmedetomidine has been evaluated in primates and rats. These studies were performed to determine if the clonidine-like pharmacological activity (that is, it exerts hypertensive effects, heart rate lowering effects, and analgesic effects) of dexmedetomidine also extends to dependence potential that clonidine has demonstrated in preclinical studies. Preclinical studies have demonstrated that clonidine can function as a positive reinforcer in primates, produces physical dependence and suppresses morphine withdrawal signs. The sponsor performed two preclinical studies to specifically address the dependence-producing potential of dexmedetomidine and three studies to characterize the overt behavioral effects associated with the acute administration of dexmedetomidine in rats and primates. Dexmedetomidine's ability to function as a positive reinforcer was assessed in rhesus monkeys. The ability of dexmedetomidine to produce physical dependence and to suppress morphine withdrawal signs were evaluated in rats.

*Clonidine is not controlled in CSA.*

##### Study 1. Gross Behavior Observation of Acute Effects in Rhesus Monkeys.

**Objective.** To characterize the acute central nervous system effects of dexmedetomidine in rhesus monkeys following intravenous and subcutaneous administration; and to determine the appropriate doses to use for the primate self-administration study.

**Procedure.** The overt behavioral effects associated with acute administration of dexmedetomidine were characterized in rhesus monkeys following intravenous and subcutaneous administration. Six rhesus monkeys, males and females weighing between 4.3 and 7.5 kg, were subjects for this study. The monkeys were randomly selected to

receive a particular dose of dexmedetomidine or saline. Each subject received seven doses of dexmedetomidine; each dose was separated by 6 days or more. Dexmedetomidine was evaluated at 0.0625, 0.25, 1.0, 4.0, and 8.0 µg/kg following intravenous administration; three subjects were tested at each dose. Following subcutaneous administration, dexmedetomidine was tested at 4.0, 8.0 and 16.0 µg/kg; three or four monkeys were tested at each dose. Saline served as the control; saline was tested at 0.25 ml/kg. Six monkeys served as control following the intravenous route and five monkeys were tested with saline following the subcutaneous route.

**Observation/Data Analysis.** The following observations were examined during the study:

- a. **Overt Behavioral Signs.** Observation for signs of dexmedetomidine-related overt behavioral signs were performed under blind conditions prior to drug administration, immediately after drug treatment, and at 15 min, 30 min, and 1 hour after dosing, and then once every 1 hr for 5 or 6 hrs after dosing. It was noted that behavioral signs were not measured immediately after subcutaneous administration. Scoring involved noting each occurrence of the following signs:

BEHAVIORS	SCALE USED TO SCORE BEHAVIOR	POSTURES	SCALE USED TO SCORE POSTURE
Salivation	4-level scale	Continual Movement	2-level scale
Retching	4-level scale	Crouching Posture	3-level scale
Vomiting	4-level scale	Lying Down	3-level scale
Eye-Closing	4-level scale	Slowed Motion	4-level scale
Pupil Size	Measurd by visual inspection	Ataxia	4-level scale
Aggression To The Observer	4-level scale		
Hypoactiivty to the Observer	2-level scale		
Grimacing At The Observer	4-level scale		

2-level scale: assigned either a - or + score; 3-level scale: assigned a -, +, or ++ score;  
 4-level score: assigned a -, +, ++, or +++ score

- b. **Food Consumption.** Food intake was recorded on a 4-level scale at 5.5 hrs after dosing and the next day (at 22 hrs after dosing).

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**RESULTS.**

Overt behavioral effects were observed in rhesus monkeys following the acute intravenous and subcutaneous administration of dexmedetomidine. Dexmedetomidine-induced behavioral effects were dose-dependent. The no effect doses following intravenous administration were 0.0625  $\mu\text{g}/\text{kg}$  and 1.0  $\mu\text{g}/\text{kg}$ . Increased aggression (2 out of 3 monkeys), and hypoactivity (1 out of 3 monkeys) were noted after 0.25  $\mu\text{g}/\text{kg}$  dexmedetomidine. Hypoactivity, eye-closing, and crouching posture were observed in all three monkeys tested with 4.0  $\mu\text{g}/\text{kg}$  and 8.0  $\mu\text{g}/\text{kg}$  intravenous dexmedetomidine administration. Slowed motion, ataxia, hyporeactivity to observer, decreased aggression to observer and salivation were also observed in 2 of the 3 monkeys following both the 4.0  $\mu\text{g}/\text{kg}$  and 8.0  $\mu\text{g}/\text{kg}$  doses of dexmedetomidine. These overt behavioral effects were also observed in some of the monkeys after being dosed with 8.0  $\mu\text{g}/\text{kg}$  of dexmedetomidine: lying down, decreased grimacing at observer, decreased aggression to observer, and salivation. Most of these behaviors were observed within 15 minutes after dosing and had disappeared within 3 hours after the 4.0  $\mu\text{g}/\text{kg}$  dose and within 5 hours after the 8.0  $\mu\text{g}/\text{kg}$  dose of dexmedetomidine.

Similar results were observed when dexmedetomidine (4.0, 8.0, and 16.0  $\mu\text{g}/\text{kg}$ ) was administered subcutaneously. Following the administration of 4.0  $\mu\text{g}/\text{kg}$  dexmedetomidine, eye closing and crouching posture were observed in 2 of the 3 monkeys tested. Eye-closing were observed in all three monkeys dosed with 8.0  $\mu\text{g}/\text{kg}$  dexmedetomidine. Two of the three monkeys displayed hypoactivity and less grimacing at observer following this dose of dexmedetomidine. In addition to these behavioral changes, hyporeactivity to the observer, slowed motion, ataxia, and decreased continual movement were observed in one monkey. Following 16.0  $\mu\text{g}/\text{kg}$  dexmedetomidine, eye-closing, hyporeactivity to observer, ataxia, and slowed motion were observed in all four monkeys. One monkey also showed decreased continual movement, decreased aggression to observer, and was lying down at this high dose of dexmedetomidine.

**Conclusion.** Acute CNS effects were observed in rhesus-monkeys following intravenously and subcutaneously administered dexmedetomidine. Dexmedetomidine-induced behavioral effects included: eye-closing, hyporeactivity to the observer, less grimacing at observer, hypoactivity, slowed motion, ataxia, and crouching posture.

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**Study 2. Tests of suppression of morphine withdrawal signs in rhesus monkeys.**

**Objective.** To determine whether or not dexmedetomidine possesses opioid type physical dependence as demonstrated by its ability to suppress morphine withdrawal signs in rhesus monkeys.

**METHODS.**

**Subjects.** Six rhesus monkeys (*Macaca Mulatta*), males and females, weighing between 4.7 to 5.4 kg and between the age of 7 to 13 years served as subjects for the study. The monkeys were housed individually.

**Dosing Regimen.** Morphine was administered subcutaneously once a day (around 9:30 a.m.) at a dose of 3.0 mg/kg for 2 weeks. During weeks 3 and 4 of the study, morphine (3.0 mg/kg) dosing was increased to twice daily (around 9:30 a.m. and 4:00 p.m.). The dose of morphine was increased to 6.0 mg/kg for the next 8 weeks or more.

**Substitution and Withdrawal Phase.** After the development and maintenance of physical dependence, the monkeys were withdrawn from morphine for about 22.0 to 22.5 hours. During this withdrawal phase, the signs of withdrawal were graded. Monkeys displaying intermediate or severe withdrawal signs were used for the suppression (i.e., substitution) tests. During each suppression test, one monkey received 0.25 or 0.5 ml/kg (s.c.) of saline. The other five monkeys received dexmedetomidine (8.0 or 16.0 µg/kg, s.c.) or codeine (16.0 or 24.0 µg/kg). The monkeys were observed for signs of withdrawal prior to the substitution test, at 15 min, 30 min, 1 hr, 2 hrs., and 3 hrs after dosing.

**Data Analysis.** Signs of withdrawal were scored during the substitution and withdrawal phase of the study. Using a 2-level (-,+), 3-level (-,+, ++), or 4-level (-, +, ++, +++) rating scale, each monkey's sign of withdrawal was scored and assigned a score. The score in each behavioral observation (See Table on page 8) was converted from the recorded levels of -, +, ++, +++, to values of 0, 1, 2, and 3, respectively. The value was then multiplied by a factor of 0-60 depending on the item. The total number of points was calculated by adding each of the weighed values and the grade of the withdrawal signs was classified as mild, intermediate or severe depending on the total scores. The degree of morphine withdrawal signs were classified as following:

CRITERIA FOR GRADING MORPHINE WITHDRAWAL SIGNS	
Grade	Total Points
Mild	≤ 15
Intermediate	16 - 30
Intermediate or severe depending on the signs observed <sup>a</sup>	31 - 40
Severe	≥ 41

a: If at least one severe sign was observed, the morphine withdrawal was graded as "severe"

The degree of withdrawal signs suppression was calculated as the Percent Suppression Score =  $100 \times (A-B)/A$ . "A" is the total number of points before the administration of dexmedetomidine or codeine. "B" is the minimum total number of points after administration. The grades of suppression of withdrawal signs were classified as following:

<b>CRITERIA FOR DEGREE OF SUPPRESSION OF WITHDRAWAL SIGNS</b>	
<b>Degree of Suppression</b>	<b>Suppression Score</b>
<b>None</b>	<b>&lt; 25%</b>
<b>Mild</b>	<b>25--&lt; 50%</b>
<b>Intermediate</b>	<b>50 - 75%</b>
<b>Marked</b>	<b>75 - ≤ 100%</b>

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## Behaviors Observed During Withdrawal Phase

GRADE	BEHAVIORAL OBSERVATION	POINTS		
		+	++	+++
MILD	Apprehension	1	2	3
	Yawning	1	2	3
	Rhinorrhea	1	2	3
	Lacrimation	1	2	3
	Shivering	1	2	3
	Twitching of the whole body	1	2	3
	Perspiration on the face	1	2	3
	Chattering	1	2	3
	Quarreling and fighting	1	2	3
INTERMEDIATE	Intention Tremor	2	4	6
	Anorexia	2	4	6
	Restlessness	2	4	c
	Pilomotor Activity	2	4	6
	Muscle Twitching and Rigidity	2	4	d
	Holding The Abdomen	2	4	6
SEVERE	Extreme Restlessness	9		
	Assumption of Peculiar Attitudes	3	6	9
	Retching	6	9	9
	Vomiting	9	9	9
	Severe Diarrhea	9		
	Erection and Continued Masturbation	3	6	9
	Inflammation of the Eyelids and Conjunctiva	3	6	9
	Continual Calling and Crying	3	6	9
	Lying on the side with eyes closed	3	6	9
	Marked Spasticity	9		
VERY SEVERE	Docility in the normally excitable animal	12		
	Dyspnea	12		
	Pallor	4	8	12
	Strabismus	4	8	12
	Dehydration	12		
	Prostration	12		
	Circulatory Collapse	12		
	Death	60		

c: Scored as "extreme restlessness";

d: Scored as "marked spasticity"

## RESULTS.

After dosing with morphine was terminated, only four (Monkeys Number: 1350 (♀), 1377 (♀), 1368 (♂), and 1409 (♂)) out of the six monkeys' morphine signs were graded as intermediate or severe. The remaining two monkeys' morphine withdrawal signs were graded as "mild"; these monkeys were not used in the substitution test. The withdrawal signs mainly associated with termination of morphine included: apprehension, chattering, twitching of the whole body, intention tremors, restlessness, pilomotor activity, muscle twitching and rigidity, holding of the abdomen, retching, and quarreling and fighting. Marked spasticity, extreme restlessness and vomiting were observed in some of the monkeys.

*Discussion*  
Results from this study have shown that dexmedetomidine does possess opioid-like activity in rhesus monkeys. *Result* As depicted in Tables 1, 2, and 3, dexmedetomidine substituted for morphine during the withdrawal phase. Prior to dexmedetomidine administration, both monkeys' withdrawal signs were graded as intermediate. Following the administration of 8.0 µg/kg of dexmedetomidine, the degree of suppression of morphine withdrawal signs was graded as mild (47.2%) and intermediate (50%) in monkey 1350 and monkey 1368, respectively. The 8.0 µg/kg dose of dexmedetomidine reduced the withdrawal score of some of the behavioral signs of morphine withdrawal. When monkey 1350 received 8.0 µg/kg dexmedetomidine (Table 1), the withdrawal score for restlessness and twitching of the whole body was lowered at 0.25, 0.5, and 1.0 hr post-dosing; restlessness was also reduced at 3 hrs observation time point. Assumption of peculiar attitudes' score was lowered at 1.0 and 3.0 hrs post-dosing (Table 1). This dose of dexmedetomidine enhanced the score assigned to pilomotor activity and retching at 2 and 3 hrs, and 3 hrs post-dosing, respectively.

*Results*  
The withdrawal score for pilomotor activity and retching was reduced at 0.5, 1.0, 2.0, and 3.9 and at 0.25, 0.5, and 3.0 hrs after dexmedetomidine, respectively in monkey 1368 (Table 2). Holding the abdomen was not observed at 0.5 hrs after dexmedetomidine administration but returned to pre-dosing level at 1 hr post-treatment and persisted throughout the observation period. The withdrawal score for chattering, twitching of the whole body, muscle twitching and rigidity, and erection and continual masturbation was increased in monkey 1368 after treatment with 8.0 µg/kg of dexmedetomidine.

The degree of suppression of morphine withdrawal signs was only slightly higher by increasing the dose of dexmedetomidine to 16.0 µg/kg. This dose of dexmedetomidine suppressed morphine withdrawal signs by 58% (intermediate) in monkey 1377 (Table 3) and by 26.1% (mild) in monkey 1350 (Table 1). However, it should be pointed out that because of the study design, that is testing different monkeys with different doses and not all monkeys with both doses, characterization of the dose-effect relationship is difficult. The withdrawal score for apprehension, twitching of the whole body, muscle twitching and rigidity, and retching was reduced in monkey 1377. Assumption of peculiar attitudes was abolished by 16.0 µg/kg dexmedetomidine. The withdrawal score was decreased at 0.25, 0.5, 1.0, and 2 hrs post-dosing in monkey 1350. The reduction in the total withdrawal score at these observation times was the result of the score for the following withdrawal signs being reduced: apprehension, chattering, and holding the abdomen. The withdrawal score at the 3 hr post-dosing observation time was higher because the score for muscle twitching and rigidity, and muscle spasticity was higher.

The ability of codeine (16.0 and 24.0 mg/kg) to suppress morphine withdrawal signs was assessed in monkeys 1350, 1368, and 1409. In contrast to the suppressing effects of dexmedetomidine, codeine was more effective in suppressing morphine's withdrawal signs (Tables 4, 5, 6, and 7). Both doses of codeine effectively suppressed the withdrawal signs associated with morphine. Codeine, at a dose of 16.0 mg/kg, suppressed morphine withdrawal signs by 65.4% (intermediate suppression), and by 80.5% (marked suppression) in monkeys 1350 and 1409, respectively. Morphine withdrawal signs were suppressed by 78.3% (marked suppression), and 82.4% (marked suppression) by 24.0 mg/kg in monkeys 1368 and 1409, respectively.

Following the administration of 16.0 mg/kg of codeine, the score assigned to chattering, twitching of the whole body, intention tremor, restlessness, pilomotor activity, assumption of peculiar attitudes, muscle twitching and rigidity, quarreling and fighting, and muscle spasticity were reduced or not present at some of the observation times in monkey 1409 (Table 6). Apprehension and holding the abdomen which was not evident before codeine (16.0 mg/kg) administration became evident at 0.25, 2, and 3 hrs post-dosing, respectively.

Codeine, 16 mg/kg, abolished the withdrawal score for twitching of the whole body, restlessness, and holding the abdomen during the 0.25-1 hr, 0.25 - 2 hr, and 0.5 - 2 hr observation period in monkey 1350, respectively (Table 4). Assumption of peculiar attitudes was not evident after codeine administration.

When the dose of codeine was increased to 24.0 mg/kg, codeine markedly suppressed morphine withdrawal signs in monkey 1368 (Table 5); chattering, restlessness, holding the abdomen, and assumption of peculiar attitudes were suppressed 100%. Apprehension, twitching of the whole body, intention tremor, and muscle twitching and rigidity were reduced at several observation time points. Codeine, 24.0 mg/kg, suppressed morphine withdrawal sign by 100% or reduced the score in monkey 1409 (Table 7). Yawning, chattering, intention tremor, assumption of peculiar attitudes, quarreling and fighting, and muscle spasticity were suppressed 100%. Pilomotor activity and muscle twitching and rigidity were reduced at some of the observation times.

**Conclusion.** Results from this study have shown that both dexmedetomidine and codeine possess cross-dependence potential for morphine. Both drugs partially substituted for morphine in morphine-dependent primates. Dexmedetomidine and codeine were effective in abolishing or reducing the score of the morphine withdrawal signs. The degree of suppression of morphine withdrawal sign observed following dexmedetomidine ranged from mild to intermediate. Codeine suppressed the withdrawal signs intermediately or markedly. *Conclusions about*  
*depression of physical dependence possible other interpretations*

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Table 1. Results from the substitution of Dexmedetomidine (8.0 µg/kg, s.c.) in Monkey N<sup>o</sup>. 1350 after withdrawal from morphine.

WITHDRAWAL SIGN	SCORE OF THE WITHDRAWAL SIGN (POINT ASSIGNED TO SCORE)											
	DEXMEDETOMIDINE: 16.0 µg/kg						DEXMEDETOMIDINE: 8.0 µg/kg					
	Time After Dosing (hr)						Time After Dosing (hr)					
	Before	0.25	0.5	1	2	3	Before	0.25	0.5	1	2	3
Apprehension	+++ (3)	++ (2)	++ (2)	++ (2)	++ (2)	+++ (3)	+++ (3)	+++ (3)	+++ (3)	+++ (3)	+++ (3)	+++ (3)
Chattering	++ (2)	+(1)	+(1)	++ (2)	++ (2)	++ (2)	+(1)	+(1)	+(1)	+(1)	+(1)	+(1)
Twitching of the whole Body	+(1)	+(1)	+(1)	+(1)	+(1)	+(1)	++ (2)	+(1)	+(1)	+(1)	++ (2)	++ (2)
Intention Tremor	++ (2)	++ (2)	++ (2)	++ (2)	++ (2)	++ (2)	+(2)	+(2)	+(2)	+(2)	+(2)	+(2)
Restlessness	- (0)	- (0)	- (0)	- (0)	- (0)	+(2)	++ (4)	+(2)	+(2)	+(2)	++ (4)	+(2)
Pilomotor Activity	+(2)	+(2)	+(2)	+(2)	+(2)	+(2)	+(2)	+(2)	+(2)	+(2)	++ (4)	++ (4)
Muscle Twitching and Rigidity	++ (4)	++ (4)	++ (4)	++ (4)	++ (4)	+++ (9)	+++ (9)	+++ (9)	+++ (9)	+++ (9)	+++ (9)	+++ (9)
Holding the Abdomen	+++ (6)	+++ (6)	+++ (6)	+++ (6)	++ (4)	++ (4)	- (0)	+(2)	- (0)	+(2)	- (0)	+(2)
Assumption of peculiar attitudes	+(3)	- (0)	- (0)	- (0)	- (0)	- (0)	+(3)	+(3)	+(3)	- (0)	+(3)	- (0)
Retching	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	++ (9)
Erection and Continual Masturbation	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)
Quarreling and fighting	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	+(1)	+(1)	+(1)	+(1)	+(1)	+(1)
Marked Spasticity	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	+(9)	+(9)	- (0)	+(9)	+(9)	+(9)
Extreme Restlessness	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)
Vomiting	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)
<b>TOTAL POINTS</b>	23	18	18	20	17	34	36	28	19	32	38	44
<b>GRADE OF WITHDRAWAL SIGNS</b>	<b>IMMEDIATE</b>						<b>SEVERE</b>					
<b>DEGREE OF SUPPRESSION</b>	100 x (23-17)/23 = 26.1% "MILD"						100 x (36-19)/36 = 47.2% "MILD"					

Table 2. Results from the substitution of Saline and Dexmedetomidine (8.0 µg/kg, s.c.) in Monkey N°. 1368 after withdrawal from morphine.

WITHDRAWAL SIGN	SCORE OF THE WITHDRAWAL SIGN (POINT ASSIGNED TO SCORE)											
	SALINE (0.5 ml/kg)						DEXMEDETOMIDINE: 8.0 µg/kg					
	Time After Dosing (hr)						Time After Dosing (hr)					
	Before	0.25	0.5	1	2	3	Before	0.25	0.5	1	2	3
Apprehension	+++ (3)	+++ (3)	++ (2)	++ (2)	+++ (3)	+++ (3)	+++ (3)	+++ (3)	+++ (3)	+++ (3)	+++ (3)	+++ (3)
Chattering	++ (2)	++ (2)	+ (1)	+ (1)	++ (2)	++ (2)	+ (1)	+ (1)	+ (1)	++ (2)	++ (2)	++ (2)
Twitching of the whole Body	+ (1)	+ (1)	+ (1)	+ (1)	++ (2)	++ (2)	+ (1)	+ (1)	+ (1)	++ (2)	++ (2)	++ (2)
Intention Tremor	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)
Restlessness	- (0)	- (0)	++ (4)	+++ (9)	+++ (9)	+++ (9)	+ (2)	++ (4)	+ (2)	+ (2)	+ (2)	+ (2)
Pilomotor Activity	+++ (4)	++ (4)	++ (4)	++ (4)	++ (4)	++ (4)	++ (4)	++ (4)	+ (2)	+ (2)	+ (2)	+ (2)
Muscle Twitching and Rigidity	++ (4)	++ (4)	+ (2)	++ (4)	+++ (9)	+++ (9)	+ (2)	++ (4)	+ (2)	+ (2)	++ (4)	++ (4)
Holding the Abdomen	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	+ (2)	+ (2)	- (0)	+ (2)	+ (2)	+ (2)
Assumption of peculiar attitudes	+ (3)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	+ (3)	- (0)	+ (3)	+ (3)	+ (3)
Retching	- (0)	- (0)	- (0)	- (0)	+++ (9)	- (0)	+++ (9)	- (0)	- (0)	+ (6)	- (0)	+ (6)
Erection and Continual Masturbation	- (0)	- (0)	- (0)	- (0)	+ (3)	+ (3)	- (0)	- (0)	- (0)	- (0)	- (0)	+ (2)
Quarreling and fighting	- (0)	- (0)	- (0)	+ (1)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)
Marked Spasticity	- (0)	- (0)	- (0)	- (0)	+ (9)	+ (9)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)
Extreme Restlessness	- (0)	- (0)	- (0)	+ (9)	+ (9)	+ (9)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)
Vomiting	- (0)	- (0)	- (0)	- (0)	+++ (9)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)
<b>TOTAL POINTS</b>	19	16	16	24	70	52	26	24	13	26	22	31
<b>GRADE OF WITHDRAWAL SIGNS</b>	<b>MILD</b>						<b>SEVERE</b>					
<b>DEGREE OF SUPPRESSION</b>	100 x (19-16)/19 = 15.8% "NONE"						100 x (26-13)/26 = 50.0% "INTERMEDIATE"					

Table 3. Results from the substitution of Saline and Dexmedetomidine (16.0 µg/kg, s.c.) in Monkey N°. 1377 after withdrawal from morphine.

WITHDRAWAL SIGN	SCORE OF THE WITHDRAWAL SIGN (POINT ASSIGNED TO SCORE)												
	SALINE (0.25 ml/kg)						DEXMEDETOMIDINE: 16.0 µg/kg						
	Time After Dosing (hr)						Time After Dosing (hr)						
	Before	0.25	0.5	1	2	3	Before	0.25	0.5	1	2	3	
Apprehension	+ (1)	+ (1)	+ (1)	+ (1)	+ (1)	+ (1)	++ (2)	+ (1)	+ (1)	+ (1)	++ (2)	++ (2)	
Chattering	+ (1)	+ (1)	+ (1)	+ (1)	+ (1)	+ (1)	+ (1)	+ (1)	+ (1)	+ (1)	+ (1)	+ (1)	
Twitching of the whole Body	++ (2)	++ (2)	++ (2)	++ (2)	++ (2)	++ (2)	++ (2)	+ (1)	+ (1)	- (0)	+ (1)	+ (1)	
Intention Tremor	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	
Restlessness	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	
Pilomotor Activity	+ (2)	- (0)	- (0)	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	
Muscle Twitching and Rigidity	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	++ (4)	+ (2)	- (0)	- (0)	- (0)	+ (2)	+ (2)	
Holding the Abdomen	++ (4)	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	++ (4)	++ (4)	++ (4)	++ (4)	++ (4)	++ (4)	
Assumption of peculiar attitudes	- (0)	- (0)	- (0)	- (0)	+ (3)	+ (3)	+ (3)	+ (3)	- (0)	- (0)	- (0)	- (0)	
Retching	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	+ (6)	- (0)	- (0)	- (0)	- (0)	- (0)	
Erection and Continual Masturbation	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	
Quarreling and fighting	+++ (3)	+++ (3)	+++ (3)	+++ (3)	+++ (3)	+++ (3)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	
Marked Spasticity	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	
Extreme Restlessness	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	
Vomiting	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	
<b>TOTAL POINTS</b>	17	13	13	15	18	20	24	14	11	10	14	14	
<b>GRADE OF WITHDRAWAL SIGNS</b>	<b>MILD</b>						<b>IMMEDIATE</b>						
<b>DEGREE OF SUPPRESSION</b>	$100 \times (17-13)/17 = 23.5\% \text{ "NONE"}$						$100 \times (24-10)/24 = 58.3\% \text{ "INTERMEDIATE"}$						

Table 4. Results from the substitution of Saline and Codeine (16.0 mg/kg, s.c.) in Monkey N<sup>o</sup>. 1350 after withdrawal from morphine.

WITHDRAWAL SIGN	SCORE OF THE WITHDRAWAL SIGN (POINT ASSIGNED TO SCORE)											
	SALINE						CODEINE: 16.0 mg/kg					
	Time After Dosing (hr)						Time After Dosing (hr)					
	Before	0.25	0.5	1	2	3	Before	0.25	0.5	1	2	3
Apprehension							+++ (3)	++ (2)	++ (2)	++ (2)	+++ (3)	+++ (3)
Chattering							++ (2)	+ (1)	+ (1)	+ (1)	+ (1)	+ (1)
Twitching of the whole Body							+++ (3)	-(0)	-(0)	-(0)	+ (1)	+ (1)
Intention Tremor							+ (2)	+ (2)	+ (2)	+ (2)	+ (2)	+ (2)
Restlessness							++ (4)	-(0)	-(0)	-(0)	-(0)	+ (2)
Pilomotor Activity							-(0)	-(0)	-(0)	-(0)	-(0)	-(0)
Muscle Twitching and Rigidity							++ (4)	++ (4)	++ (4)	++ (4)	++ (4)	++ (4)
Holding the Abdomen							+ (2)	+ (2)	-(0)	-(0)	-(0)	+ (2)
Assumption of peculiar attitudes							++ (6)	-(0)	-(0)	-(0)	-(0)	-(0)
Retching							-(0)	-(0)	-(0)	-(0)	-(0)	-(0)
Erection and Continual Masturbation							-(0)	-(0)	-(0)	-(0)	-(0)	-(0)
Quarreling and fighting							-(0)	-(0)	-(0)	-(0)	-(0)	-(0)
Marked Spasticity							-(0)	-(0)	-(0)	-(0)	(0)-	-(0)
Extreme Restlessness							-(0)	-(0)	-(0)	-(0)	-(0)	-(0)
Vomiting							-(0)	-(0)	-(0)	-(0)	-(0)	-(0)
<b>TOTAL POINTS</b>							26	11	9	9	11	15
<b>GRADE OF WITHDRAWAL SIGNS</b>							<b>IMMEDIATE</b>					
<b>DEGREE OF SUPPRESSION</b>							100 x (26-9)/26 = 65.4% "INTERMEDIATE"					

Table 5. Results from the substitution of Saline and Codeine (24.0 mg/kg, s.c.) in Monkey N<sup>o</sup>: 1368 after withdrawal from morphine.

WITHDRAWAL SIGN	SCORE OF THE WITHDRAWAL SIGN (POINT ASSIGNED TO SCORE)											
	SALINE						CODEINE: 24.0 mg/kg					
	Time After Dosing (hr)						Time After Dosing (hr)					
	Before	0.25	0.5	1	2	3	Before	0.25	0.5	1	2	3
Apprehension							+++ (3)	++ (2)	-(0)	-(0)	+(1)	++ (2)
Chattering							++ (2)	-(0)	-(0)	-(0)	-(0)	-(0)
Twitching of the whole Body							+(1)	-(0)	-(0)	-(0)	-(0)	+(1)
Intention Tremor							+92)	-(0)	-(0)	-(0)	-(0)	+(2)
Restlessness							++ (4)	-(0)	-(0)	-(0)	-(0)	-(0)
Pilomotor Activity							+(2)	+(2)	+(2)	+(2)	+(2)	+(2)
Muscle Twitching and Rigidity							++ (4)	+(2)	+(2)	+(2)	+(2)	+(2)
Holding the Abdomen							+(2)	-(0)	-(0)	-(0)	-(0)	-(0)
Assumption of peculiar attitudes							+(3)	-(0)	-(0)	-(0)	-(0)	-(0)
Retching							-(0)	-(0)	-(0)	-(0)	-(0)	-(0)
Erection and Continual Masturbation							-(0)	-(0)	-(0)	-(0)	-(0)	-(0)
Quarreling and fighting							-(0)	-(0)	+(1)	+(1)	-(0)	-(0)
Marked Spasticity							-(0)	-(0)	-(0)	-(0)	-(0)	-(0)
Extreme Restlessness							-(0)	-(0)	-(0)	-(0)	-(0)	-(0)
Vomiting							-(0)	-(0)	-(0)	-(0)	-(0)	-(0)
<b>TOTAL POINTS</b>							23	6	5	5	5	10
<b>GRADE OF WITHDRAWAL SIGNS</b>							<b>IMMEDIATE</b>					
<b>DEGREE OF SUPPRESSION</b>							100 x (23-5)/23 = 78.3% "MARKED"					

Table 6. Results from the substitution of Saline and Codeine (16.0 mg/kg, s.c.) in Monkey N<sup>o</sup>. 1409 after withdrawal from morphine.

WITHDRAWAL SIGN	SCORE OF THE WITHDRAWAL SIGN (POINT ASSIGNED TO SCORE)											
	SALINE 0.5 ml/kg						CODEINE: 16.0 mg/kg					
	Time After Dosing (hr)						Time After Dosing (hr)					
	Before	0.25	0.5	1	2	3	Before	0.25	0.5	1	2	3
Yawning	- (0)	- (0)	- (0)	+ (1)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)
Apprehension	+ (1)	+ (10)	+ (1)	++ (2)	++(2)	+++ (3)	- (0)	+ (1)	- (0)	- (0)	+ (1)	+ (1)
Chattering	+ (1)	+ (1)	+ (1)	+ (1)	+ (1)	++ (2)	+ (1)	- (0)	- (0)	- (0)	- (0)	- (0)
Twitching of the whole Body	+ (1)	+ (1)	+ (1)	++ (2)	++ (2)	+++ (3)	+++ (3)	- (0)	- (0)	- (0)	+ (1)	+ (1)
Intention Tremor	- (0)	- (0)	- (0)	- (0)	- (0)	+ (2)	+ (2)	- (0)	- (0)	- (0)	- (0)	- (0)
Restlessness	+ (2)	++ (4)	+++ (9)	+++ (9)	+ (2)	+ (2)	+ (2)	- (0)	- (0)	- (0)	- (0)	- (0)
Pilomotor Activity	++ (4)	++ (4)	++ (4)	++ (4)	++ (4)	++ (4)	+++ (6)	++ (4)	++ (4)	++ (4)	++ (4)	++ (4)
Muscle Twitching and Rigidity	+++ (9)	+++ (9)	+++ (9)	+++ (9)	+++ (9)	+++ (9)	+++ (9)	++ (4)	++ (4)	++ (4)	+++ (9)	+++ (9)
Holding the Abdomen	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	+ (2)
Assumption of peculiar attitudes	+ (3)	+ (3)	++ (6)	++ (6)	+++ (9)	++ (6)	++ (6)	- (0)	- (0)	- (0)	- (0)	- (0)
Retching	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)
Erection and Continual Masturbation	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)
Quarreling and fighting	+ (1)	+ (1)	+ (1)	+ (1)	- (0)	- (0)	+++ (3)	++ (2)	- (0)	- (0)	- (0)	++ (2)
Marked Spasticity	+ (9)	+ (9)	+ (9)	+ (9)	+ (9)	+ (9)	+ (9)	- (0)	- (0)	- (0)	+ (9)	+ (9)
Extreme Restlessness	- (0)	- (0)	+ (9)	+ (9)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)
Vomiting	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)	- (0)
<b>TOTAL POINTS</b>	31	33	43	53	38	40	41	11	8	8	24	28
<b>GRADE OF WITHDRAWAL SIGNS</b>	SEVERE						SEVERE					
<b>DEGREE OF SUPPRESSION</b>	100 X (31-33)/31 = -6.5 "NONE"						100 x (41-8)/41 = 80.5 "MARKED"					

Table 7. Results from the substitution of Saline and Codeine (24.0 mg/kg, s.c.) in Monkey N<sup>o</sup>. 1409 after withdrawal from morphine.

WITHDRAWAL SIGN	SCORE OF THE WITHDRAWAL SIGN (POINT ASSIGNED TO SCORE)											
	SALINE						CODEINE: 24.0 mg/kg					
	Time After Dosing (hr)						Time After Dosing (hr)					
	Before	0.25	0.5	1	2	3	Before	0.25	0.5	1	2	3
Yawning							+ (1)	- (0)	- (0)	- (0)	- (0)	- (0)
Apprehension							- (0)	- (0)	- (0)	- (0)	- (0)	- (0)
Chattering							+ (1)	+ (1)	- (0)	- (0)	- (0)	- (0)
Twitching of the whole Body							+ (1)	+ (1)	- (0)	- (0)	- (0)	+ (1)
Intention Tremor							+ (2)	+ (2)	- (0)	- (0)	- (0)	- (0)
Restlessness							- (0)	- (0)	- (0)	- (0)	- (0)	- (0)
Pilomotor Activity							+++ (6)	+++ (6)	+++ (6)	+++ (6)	++ (4)	+++ (6)
Muscle Twitching and Rigidity							+++ (9)	+++ (9)	++ (4)	++ (4)	++ (4)	++ (4)
Holding the Abdomen							- (0)	- (0)	- (0)	- (0)	- (0)	- (0)
Assumption of peculiar attitudes							+ (3)	- (0)	- (0)	- (0)	- (0)	- (0)
Retching							- (0)	- (0)	- (0)	- (0)	- (0)	- (0)
Erection and Continual Masturbation							- (0)	- (0)	- (0)	- (0)	- (0)	- (0)
Quarreling and fighting							++ (2)	++ (2)	+ (1)	- (0)	- (0)	- (0)
Marked Spasticity							+ (9)	+ (9)	- (0)	- (0)	- (0)	- (0)
Extreme Restlessness							- (0)	- (0)	- (0)	- (0)	- (0)	- (0)
Vomiting							- (0)	- (0)	- (0)	- (0)	- (0)	- (0)
<b>TOTAL POINTS</b>							34	30	11	10	6	11
<b>GRADE OF WITHDRAWAL SIGNS</b>							<b>SEVERE</b>					
<b>DEGREE OF SUPPRESSION</b>							100 x (34-6)/34 = 82.4% "MARKED"					

**Study 3.** Continuous intravenous self-administration experiment in rhesus monkeys.

**Objectives:** To determine if dexmedetomidine can function as a positive reinforcer.

**Procedures.** Four rhesus monkeys, males and females weighing between 5.1 and 7.0 kg, served as subjects for the study. All monkeys had prior experience in drug self-administration studies. The details of the training procedure (i.e., duration of behavioral session, how many days per week they were allowed to self-administer, schedule of reinforcement) and the training drug was not described. Drug delivery was contingent on responding under a fixed-ratio schedule of reinforcement. This experiment consisted of nine testing periods:

**Test Period 1:** Saline (0.25 ml/kg/injection) was substituted in this period until the daily number of saline self-administration was reduced to 10 or less for 7 consecutive days.

**Test Period 2.** During this testing period, pentazocine (125.0  $\mu\text{g}/\text{kg}/\text{injection}$ ) was available for self-administration. The maximum number of drug injections was limited to 30 per day in order to avoid overdosing. When the monkeys achieved 29 or 30 injections per day for 3 consecutive days, saline was substituted for pentazocine. If a monkey did not show self-administration behavior by the end of the two weeks, the dose of pentazocine was increased to 250.0  $\mu\text{g}/\text{kg}/\text{injection}$ .

**Test Period 3.** Saline (0.25 ml/kg/infusion) was available until the daily number of saline self-administration was reduced to 10 or less.

**Test Period 4.** Dexmedetomidine (0.0625  $\mu\text{g}/\text{kg}/\text{infusion}$ ) was substituted for 2 or 3 weeks.

**Test Period 5.** Dexmedetomidine (0.25  $\mu\text{g}/\text{kg}/\text{infusion}$ ) was substituted for 2 or 3 weeks.

**Test Period 6.** Dexmedetomidine (1.0  $\mu\text{g}/\text{kg}/\text{infusion}$ ) was available for 2 or 3 weeks.

**Test Period 7.** Saline (0.25 ml/kg/injection) was substituted for 2 days after the highest rate of dexmedetomidine was obtained.

**Test Period 8.** The dose of dexmedetomidine that maintained the highest rate of self-administration was tested again for another 2 weeks.

**Test Period 9.** Saline substitution occurred for two weeks.

**Data Analysis.** The reviewer has analyzed the data in terms of the last 3 days of the substitution period. The dependent variable is the mean number of injections over these three last days. Pentazocine and dexmedetomidine was considered to be a positive reinforcer if the mean number of injections exceeded the average saline control (preceding the test dose) number and the ranges did not overlap.

**RESULTS.**

Dexmedetomidine functioned as a positive reinforcer in rhesus monkeys. At least one dose of dexmedetomidine maintained self-administration behavior in the subjects of this study (Table 8). The highest dose of dexmedetomidine, 1.0 µg/kg/injection, functioned as a positive reinforcer in monkey 1357, 1382, and 1392. The mean number of infusions for monkeys 1357, 1382, and 1392 was 34.3, 68.3, and 32.3 during the first substitution test, respectively. When this dose of dexmedetomidine was substituted a second time, it only maintained high rates of self-administration monkeys 1357 and 1382; the mean number of infusion was 101.7, and 65.3, respectively.

The 0.025 µg/kg/injection dose of dexmedetomidine maintained high rates of self-administration in monkey 1403. During the first substitution test, 60 to 81 infusions were obtained during the last 6 days of the substitution test. Higher rates of self-administration were observed during the second substitution test with this dose of dexmedetomidine; ranging from 81 to 196 during the last 3 days of testing. Self-administration behavior was not maintained by 0.25 µg/kg/injection of dexmedetomidine in monkeys 1357, 1382, and 1392. The lowest dose of dexmedetomidine (0.0625 µg/kg/injection) tested failed to function as a positive reinforcer in all four subjects.

Pentazocine maintained self-administration behavior in all subjects. In three subjects (1357, 1382, and 1392), pentazocine (125 µg/kg/injection) intake was 30 per day during the last 3 days of the substitution. Pentazocine at 125 µg/kg/injection failed to maintain self-administration behavior in the fourth monkey (1403). When the dose of pentazocine was increased to 250.0 µg/kg/injection, self-administration behavior was observed in monkey 1403.

**Conclusion.** Dexmedetomidine functioned as a positive reinforcer in primates. At a dose of 1.0 µg/kg, dexmedetomidine maintained self-administration behavior that was higher than those maintained by saline. A lower dose, 0.025 µg/kg, of dexmedetomidine maintained high rates of self-administration in the monkeys.

0.25 µg/kg/1403

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**Table 8. Mean (and Standard Error the Mean) Number of Self-Injection for the last 3 days of each drug condition for each monkey.**

MONKEY N <sup>o</sup>	TREATMENT CONDITION	NUMBER OF DAYS TESTED	NUMBER OF SELF- INJECTIONS OVER LAST 3 DAYS OF TESTING			$\bar{x}$ (SE)
			Day 1	Day 2	Day 3	
1357 (♂)	Saline: 0.25 ml/kg/inj	7	2	0	0	0.67 ± 1.15
	Pentazocine: 125 µg/kg/inj	6	30	30	30	30 ± 0
	Saline: 0.25 ml/kg/inj	7	2	4	0	2.0 ± 2.0
	Dexmedetomidine: 0.0625 µg/kg/inj	16	1	1	1	1 ± 0
	Dexmedetomidine: 0.25 µg/kg/inj	17	1	1	0	0.67 ± 0.58
	Dexmedetomidine: 1.0 µg/kg/inj	16	27	32	44	34.3 ± 8.7
	Saline: 0.25 ml/kg/inj	2	34	40	-	37 ± 4.2
	Dexmedetomidine: 1.0 µg/kg/inj	14	113	97	95	101.7 ± 9.9
	Saline: 0.25 ml/kg/inj	14	15	18	12	15 ± 3.0
1382 (♀)	Saline: 0.25 ml/kg/inj	7	0	1	0	0.33 ± 0.58
	Pentazocine: 125 µg/kg/inj	15	30	30	30	30 ± 0
	Saline: 0.25 ml/kg/inj	24	0	3	0	1.0 ± 1.7
	Dexmedetomidine: 0.0625 µg/kg/inj	16	0	2	0	0.67 ± 1.15
	Dexmedetomidine: 0.25 µg/kg/inj	18	0	0	0	0 ± 0
	Dexmedetomidine: 1.0 µg/kg/inj	15	58	65	82	68.3 ± 12.3
	Saline: 0.25 ml/kg/inj	2	14	15	-	15 ± 1.4
	Dexmedetomidine: 1.0 µg/kg/inj	15	68	53	75	65.3 ± 11.2
	Saline: 0.25 ml/kg/inj	14	10	4	2	5.3 ± 4.2

Table 8 (cont.). Mean (and Standard Error of the Mean) Number of Self-Injection for the last 3 days of each drug condition for each monkey.

MONKEY Nº	TREATMENT CONDITION	NUMBER OF DAYS TESTED	NUMBER OF SELF-INJECTIONS OVER LAST 3 DAYS OF TESTING			$\bar{x}$ (SE)
			Day 1	Day 2	Day 3	
1392 (♂)	Saline: 0.25 ml/kg/inj	7	0	1	0	0.33 ± 0.58
	Pentazocine: 125 µg/kg/inj	11	30	30	30	30 ± 0
	Saline: 0.25 ml/kg/inj	15	3	5	5	4.3 ± 1.2
	Dexmedetomidine: 0.0625 µg/kg/inj	14	1	6	2	3.0 ± 2.6
	Dexmedetomidine: 0.25 µg/kg/inj	21	20	113	11	14.7 ± 4.7
	Dexmedetomidine: 1.0 µg/kg/inj	22	48	23	26	32.3 ± 13.7
	Saline: 0.25 ml/kg/inj	2	23	26	-	24.3 ± 2.1
	Dexmedetomidine: 1.0 µg/kg/inj	14	8	7	19	11.3 ± 6.7
	Saline: 0.25 ml/kg/inj	22	15	9	7	10.3 ± 4.2
1403 (♂)	Saline: 0.25 ml/kg/inj	7	0	0	0	0 ± 0
	Pentazocine: 125 µg/kg/inj	14	1	0	0	0.33 ± 0.58
	Pentazocine: 250 µg/kg/inj	11	29	30	29	29.3 ± 0.58
	Saline: 0.25 ml/kg/inj	0	4	3	1	2.7 ± 1.53
	Dexmedetomidine: 0.0625 µg/kg/inj	16	1	0	0	0.33 ± 0.58
	Dexmedetomidine: 0.25 µg/kg/inj	15	76	80	75	77 ± 2.6
	Saline: 0.25 ml/kg/inj	2	37	27	-	32 ± 7.0
	Dexmedetomidine: 0.25 µg/kg/inj	14	81	159	196	145 ± 58.7
	Saline: 0.25 ml/kg/inj	14	12	15	9	12 ± 3.0

**Study 4. Gross Behavior Observation of Acute Effects in Rats.**

**Objective.** To characterize the acute effects of dexmedetomidine in rats following intravenous administration.

**Procedure.**

Twenty four rats weighing between 254 and 269 grams were subjects for this study. The rats were randomly assigned to the saline or dexmedetomidine groups. Dexmedetomidine was tested at 1.0, 4.0, 8.0 and 16.0  $\mu\text{g}/\text{kg}$ ; four rats were tested per dose. Saline served as control. Saline was tested in six rats at 2 ml/kg.

Overt behavioral signs were observed once prior to dosing, immediately after dosing and at 15 min, 30 min, and every hour up to 4 hours post-dosing. Behavioral signs observed and scored, using the 2-level scale (-, +) were:

BEHAVIORS OBSERVED IN CAGE	BEHAVIORS OBSERVED DURING AND AFTER RATS WERE LIFTED AND RELEASED BY OBSERVER
Continual Movement	Salivation
Lying Down	Hypersensitivity or Hyporeactivity To External Stimulus
Eye-Closing	Slowed Motion
Piloerection	Ataxia
	Muscle Relaxation
	Ptosis

**Results.**

Dexmedetomidine elicited overt behavioral signs in rats following intravenous administration. Results are summarized in Table 9. Following the administration of intravenous saline, no behavioral changes were noted in most rats. Hyperreactivity was observed in three of the rats (259, 260, and 269) 0.5 hours after dosing and increased urination was observed in one rat (260).

The number of rats presenting with dexmedetomidine-induced behavioral signs and the number of behavioral effects noted was dose-dependent. The two lowest doses of dexmedetomidine (1.0 and 4.0  $\mu\text{g}/\text{kg}$ ) were without any significant effects. One rat displayed hyperreactivity immediately after receiving 1.0  $\mu\text{g}/\text{kg}$  of dexmedetomidine. Dexmedetomidine at a dose of 4.0  $\mu\text{g}/\text{kg}$  did not elicit any overt behavioral effects in any of the subjects. Because rat 259 displayed hyperreactivity prior to dosing, it is reasonably safe to conclude that the hyperreactivity observed after drug treatment was not drug-related.

Ataxia, deep respiration, hyperreactivity and crawling were observed following intravenous administration of 8.0  $\mu\text{g}/\text{kg}$  dexmedetomidine. Ataxia was observed in two (267 and 269) of the four rats tested immediately after dosing. Rat 267 was ataxic and displayed deep respiration 0.25 hrs after dosing. Immediately after dosing, rat 269 was ataxic, and observed crawling; at 0.25 hrs after dosing these effects were diminished and hyperreactivity was observed.

Following the intravenous administration of 16.0 µg/kg dexmedetomidine, laying down, deep respiration, crawling, ataxia, hyperreactivity, ptosis, hyporeactivity, slowed motion, and urination were observed. Many of these behavioral effects occurred immediately after dosing and persisted for up to 1 or 3 hours.

**Conclusion.** Results from this study have demonstrated that overt behavioral signs are produced by dexmedetomidine following intravenous administration. Ataxia, deep respiration, and hyperreactivity were the most prominent behavioral signs observed.

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Table 9. Overt Behavioral Effects observed following a single-dose intravenous administration of saline and dexmedetomidine in rats.

BEHAVIORAL SIGN	NUMBER OF RATS SHOWING EACH BEHAVIORAL SIGN																	
	TIME AFTER DOSING										TIME AFTER DOSING							
	SALINE: 2 ml/kg (N=6)										DEXMEDETOMIDINE: 1 µg/kg (N = 4)							
	Before	0	0.25	0.5	1.0	2.0	3.0	4.0	0.5	N	Before	0	0.25	0.5	1.0	2.0	3.0	4.0
Continual Movement	0	0	0	0	0	0	0	0	0	N	0	0	0	0	0	0	0	0
Lying Down	0	0	0	0	0	0	0	0	0	N	0	0	0	0	0	0	0	0
Eye -Closing	0	0	0	0	0	0	0	0	0	N	0	0	0	0	0	0	0	0
Piloerection	0	0	0	0	0	0	0	0	0	N	0	0	0	0	0	0	0	0
Salivation	0	0	0	0	0	0	0	0	0	N	0	0	0	0	0	0	0	0
Hyperreactivity	1	1	2	3	1	1	1	0	0	N	0	1	0	0	0	0	0	0
Hyporeactivity	0	0	0	0	0	0	0	0	0	N	0	0	0	0	0	0	0	0
Slowed Motion	0	0	0	0	0	0	0	0	0	N	0	0	0	0	0	0	0	0
Ataxia	0	0	0	0	0	0	0	0	0	N	0	0	0	0	0	0	0	0
Muscle Relaxation	0	0	0	0	0	0	0	0	0	N	0	0	0	0	0	0	0	0
Ptosis	0	0	0	0	0	0	0	0	0	N	0	0	0	0	0	0	0	0
Urination	0	0	1	1	1	1	1	1	0	1								

Table 9 (cont.). Overt Behavioral Effects observed following a single-dose intravenous administration of saline and dexmedetomidine in rats.

BEHAVIORAL SIGN	NUMBER OF RATS SHOWING EACH BEHAVIORAL SIGN																	
	TIME AFTER DOSING									TIME AFTER DOSING								
	DEXMEDETOMIDINE: 4 µg/kg (N=4)									DEXMEDETOMIDINE: 8 µg/kg (N = 4)								
	Before	0	0.25	0.5	1.0	2.0	3.0	4.0	0.5	Before	0	0.25	0.5	1.0	2.0	3.0	4.0	5.0
Continual Movement	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Lying Down	0	0	0	0	0	0	0	0	N	0	0	0	0	0	0	0	0	0
Eye -Closing	0	0	0	0	0	0	0	0	N	0	0	0	0	0	0	0	0	0
Piloerection	0	0	0	0	0	0	0	0	N	0	0	0	0	0	0	0	0	0
Salivation	0	0	0	0	0	0	0	0	N	0	0	0	0	0	0	0	0	0
Hyperreactivity	1	1	1	1	1	1	1	1	0	1	1	1	1	1	0	1	0	0
Hyporeactivity	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Slowed Motion	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ataxia	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0
Muscle Relaxation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ptosis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Deep Respiration										0	1	0	0	0	0	0	0	0
Crawling										0	1	0	0	0	0	0	0	0

Table 9 (cont.). Overt Behavioral Effects observed following a single-dose intravenous administration of saline and dexmedetomidine in rats.

BEHAVIORAL SIGN	NUMBER OF RATS SHOWING EACH BEHAVIORAL SIGN															
	TIME AFTER DOSING								TIME AFTER DOSING							
	DEXMEDETOMIDINE: 16 µg/kg (N=4)															
	Before	0	0.25	0.5	1.0	2.0	3.0	4.0	Before	0	0.25	0.5	1.0	2.0	3.0	4.0
Continual Movement	0	0	0	0	0	0	0	0								
Lying Down	0	4	4	1	1	0	0	0								
Eye -Closing	0	0	0	0	0	0	0	0								
Piloerection	0	0	0	0	0	0	0	0								
Salivation	0	0	0	0	0	0	0	0								
Hyperreactivity	2	1	1	2	3	2	2	2								
Hyporeactivity	0	0	1	0	0	0	0	0								
Slowed Motion	0	1	1	0	0	0	0	0								
Ataxia	0	2	2	1	0	0	0	0								
Muscle Relaxation	0	0	0	0	0	0	0	0								
Ptosis	0	0	0	1	0	0	0	0								
Urination	0	0	2	2	1	1	0	0								
Deep Respiration	0	4	4	1	0	0	0	0								
Crawling	0	0	2	1	1	0	0	0								

**Study 5. Tests of production of physical dependence by the repeated intravenous method in rats.**

**Objectives:** To characterize the physical-dependence potential of dexmedetomidine following a 3-day and 7-day infusion period in rats.

**Subjects.** Forty-eight rats weighing between 217 and 266 grams were subjects for the study. The rats were individually housed. The rats were acclimated to their housing condition for 2 to 3 days prior to the initiation of the study. Six rats were used per dose in each experiment.

**Procedure.** Prior to the induction of physical dependence, the rats were surgically prepared with a chronic cannulae into the jugular vein. Intravenous infusion of the drug was controlled by a micro PDP-11/53 computer system. The condition (i.e., patency) of the catheter was confirmed daily by a manual infusion of drug solution with a syringe. The physical dependence potential of dexmedetomidine was assessed using two different dosing regimen; a 3-day infusion dosing regimen and a 7-day infusion period.

**Three day repeated infusion experiment.** In this experiment, the rats were infused for three days with dexmedetomidine (8.0 and 16.0  $\mu\text{g}/\text{kg}/\text{infusion}$ ), pentazocine (4.0  $\text{mg}/\text{kg}/\text{infusion}$ ) or saline. Gross behavioral observation was performed daily during the 3-day infusion period. The patency of the catheter was checked daily within 1 hr before the last infusion. Within 30 min after the last infusion, the rats received a subcutaneous injection of naloxone (1.0  $\text{mg}/\text{kg}$ ). Withdrawal signs were observed every 15 min for 1 hr after naloxone administration.

**Seven day repeated infusion experiment.** The rats were infused daily for seven days with dexmedetomidine (8.0 and 16.0  $\mu\text{g}/\text{kg}/\text{infusion}$ ), pentazocine (4.0  $\text{mg}/\text{kg}/\text{infusion}$ ) or saline. Gross behavioral observation was performed daily during the 7-day infusion period. Immediately after the last drug infusion, the rats' weight was measured and withdrawal observation was performed at 1, 5, and 24 hrs after the last infusion and then at 1-day intervals for 7 days.

**Data Analysis.** The primary outcome measures for this study include: signs of withdrawal and body weight loss. Body weight loss for the 3-day infusion study was calculated as the percent change from the body weight before naloxone administration. For the 7-day infusion study it was calculated as the percent change in body weight before the initiation of chronic drug dosing and after the 7-days drug dosing. Signs of withdrawal was scored as being morphine-like during the withdrawal phase of the study. The morphine-like withdrawal signs scored were:

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SIGNS		CONDITION	POINTS
BEHAVIORAL SIGNS	Unusual Posture	-	2
	Hyperirritability	Touch Approach	1 2
	Teeth Chattering	Intermittent Continuous	0.5 1
AUTONOMIC SIGNS	Lacrimation	-	4
	Diarrhea	Soft Unshaped	4 8
	Salivation	Slight Marked	1 2
BODY WEIGHT LOSS		<2%	0
		<4%	5
		<6%	10
		<8%	15
		≥8%	20

## RESULTS.

**3-Day Infusion Study.** During the 3-day infusion study, some overt behaviors were observed in the rats infused with dexmedetomidine and pentazocine. In the saline group, only hypoactivity was observed during the infusion period. Hypoactivity, hyperreactivity, penile erection, eating behavior, lying down and piloerection were observed in the rats infused with 8.0 µg/kg of dexmedetomidine. The incidence of hypoactivity was similar to that observed in the saline-treated rats. In the 16.0 µg/kg group, lying down, muscle relaxation, hyporeactivity, hyperreactivity, straub tail, tail whipping, and slowed motion were observed. Hypoactivity was observed at a higher incidence than in the saline group.

Results from the withdrawal phase of the 3-day infusion study are presented in Figures 1 and 2. As depicted in Figure 1, in comparison to saline, there was no significant body weight loss in both dexmedetomidine treatment groups. The average body weight loss for the saline, 8.0 µg/kg dexmedetomidine, and 16.0 µg/kg dexmedetomidine groups was 1.2%, 1.1%, and 2.0%, respectively. In contrast, the mean body weight loss for the pentazocine group was statistically significantly different from the saline group. The mean body weight loss for the group was 2.8%.

With the exception of teeth chattering occurring in one rat and diarrhea in another rat, no withdrawal signs were observed in the saline group. The total withdrawal sign scores ranged between 0 and 9 with a median score of 0 for the saline group. Behavioral withdrawal signs and withdrawal signs related to the autonomic nervous system were observed in both dexmedetomidine groups (Figure 2). Hyperritability, unusual posture and teeth chattering were observed in all six rats. In 3 of the 6 rats tested, salivation and diarrhea were observed. The total withdrawal sign score for the 8.0 µg/kg dexmedetomidine group ranged between 0.5 and 15.0 with a median score of 4.5.

In the 16.0 µg/kg dexmedetomidine group, the total withdrawal sign score ranged between 4 and 19 with a median score of 12.5. Five of the six rats displayed hyperirritability, unusual posture, and teeth chattering after termination of dexmedetomidine infusion. The observed autonomic-related withdrawal signs included salivation, and diarrhea; five

of six rats elicited these responses. One death was observed in this high dose group. After the first infusion with 16.0  $\mu\text{g}/\text{kg}$  dexmedetomidine, this rat experienced accelerated respiration and then showed hypoactivity and was observed lying down. This rat died on the second day of the 3-day infusion period. Histological analysis suggested that the death was not related to dexmedetomidine. Ulcers in the gastric mucosa and hemorrhage in the lungs were noted.

In comparison to saline and dexmedetomidine, rats in the pentazocine group had a higher total withdrawal score. The total withdrawal score for the six rats in the pentazocine group ranged between 13 and 15 with a median score of 18.3. Pentazocine withdrawal syndrome was comprised of the behavioral signs unusual posture, teeth chattering and hyperirritability in all or nearly all rats, and the autonomic signs of salivation (3/6 rats) and diarrhea (5/6 rats).

**Seven-day Infusion Study.** No significant body weight loss was observed in any of the rats in the four treatment groups. During the 7-day infusion period, some overt behaviors were observed. Hypoactivity was observed in most of the rats in the four treatment groups. Lying down, hyperreactivity and piloerection were also observed in most of the rats in the 8.0  $\mu\text{g}/\text{kg}$  dexmedetomidine group. Many of the rats in the 16.0  $\mu\text{g}/\text{kg}$  dexmedetomidine group displayed hyperreactivity, hypoactivity, piloerection, and were observed lying down. During the withdrawal phase of the study, hyperirritability (graded as weak) was observed in 3 out of 6 rats in both dexmedetomidine groups; hyperirritability was observed during the first five hours after termination of the drug in most rats. One rat in the 8.0  $\mu\text{g}/\text{kg}$  dexmedetomidine group displayed hyperirritability for up to 4 days. Diarrhea (soft feces) was observed in 2 rats in the high dose dexmedetomidine group, and from the second day of the withdrawal period in the saline group.

A few withdrawal signs were manifested in some of the rats withdrawn from pentazocine. Hyperirritability (graded as weak) was observed in 4 rats, and diarrhea (soft feces) occurred in three rats. The diarrhea was observed on the first day of withdrawal in two rats and on the seventh day of the withdrawal period in the third rat.

**Conclusion.** Results from this study have demonstrated that dexmedetomidine is capable of producing physical dependence in rats after seven-days of infusion. The withdrawal syndrome was mild and was comprised of the following signs: hyperirritability, piloerection, lying down, and diarrhea. The withdrawal signs observed after 16.0  $\mu\text{g}/\text{kg}$  dexmedetomidine was similar; hence dexmedetomidine physical dependence-producing potential was equal to that of pentazocine. It is possible that the withdrawal syndrome would have been more intense if the induction phase was longer than 7 days. Traditionally, when the physical dependence potential is being characterized, the induction period usually lasts for 2 to 3 weeks.

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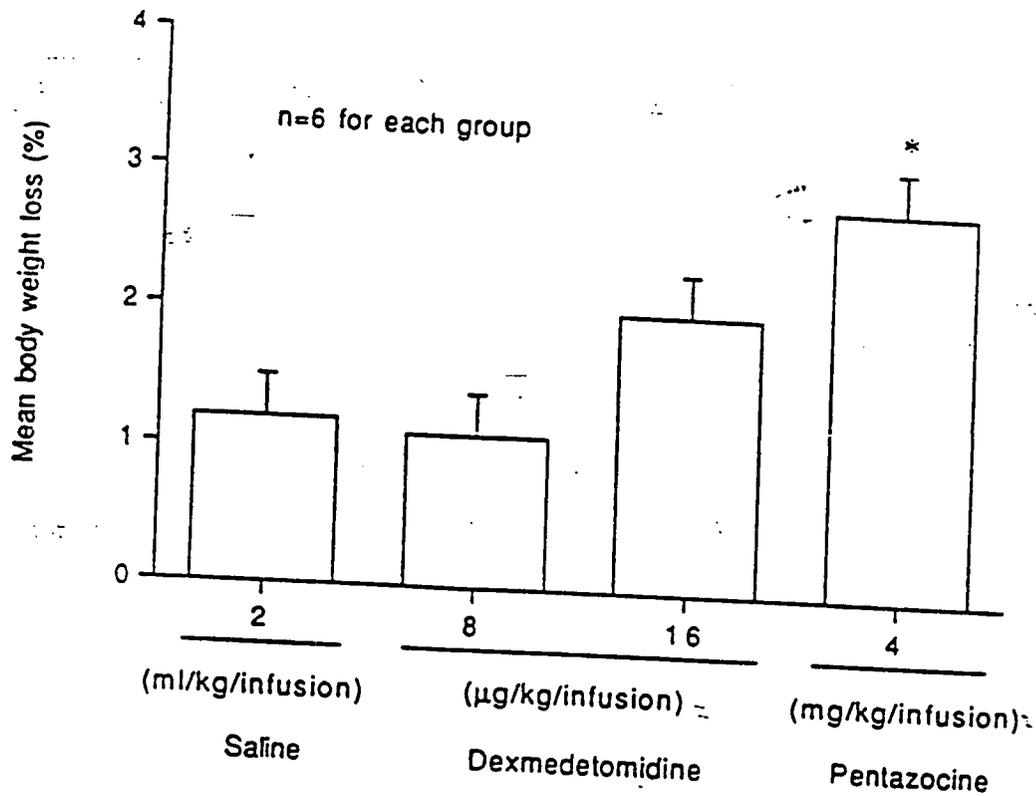


Figure 1 (As copied from the NDA). Body weight loss (%) in naloxone test after hourly infusion of saline, dexmedetomidine, and pentazocine for 3 days in rats. Naloxone 1 mg/kg, s.c. was administered 30 minutes after the intravenous infusion. Body weight loss is expressed as percentage against the value before the administration of naloxone.

\*:  $P < 0.05$  against saline (Dunnett's multiple comparison method)

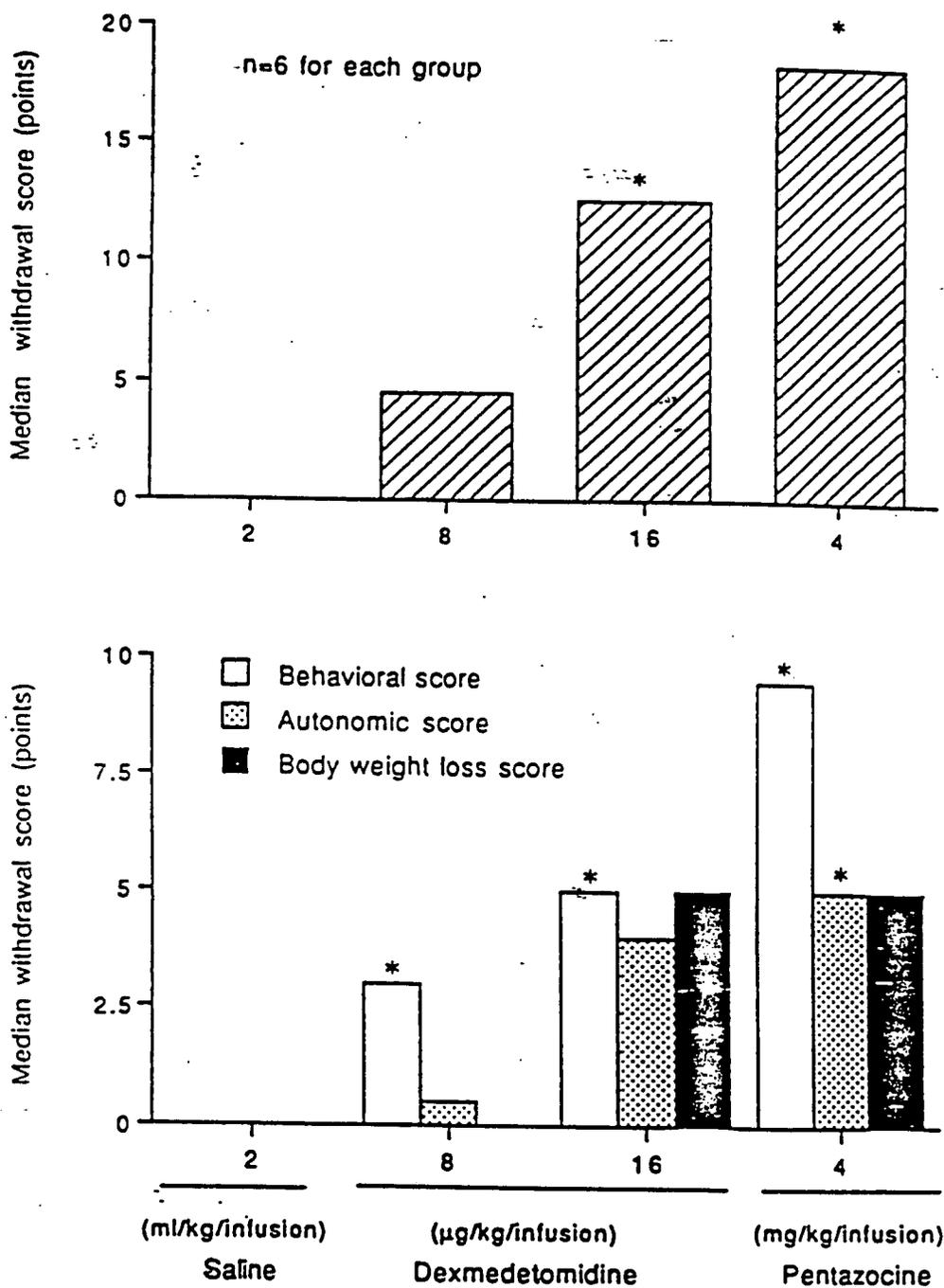


Figure 2 (As copied from the NDA). Withdrawal scores of rats in naloxone test after hourly intravenous infusion of saline, dexmedetomidine, and pentazocine for 3 days. Naloxone 1 mg/kg, s.c. was administered 30 minutes after the final intravenous infusion. Upper panel: total withdrawal score. Lower panel: behavioral, autonomic and body weight loss scores.

\*: P < 0.05 against saline (Mann-Whitney's U-test)

**CLINICAL ABUSE LIABILITY ASSESSMENT**

No clinical abuse liability studies were performed to evaluate the abuse potential of dexmedetomidine in humans. The sponsor submitted summary of the results from the following clinical studies:

- Study W97-028. Dexmedetomidine dose-ranging study to evaluate the effects of dexmedetomidine on sedation.
- Study W97-249. A Phase II, single-center, two-part study evaluating the safety, efficacy, and dose-titratability of dexmedetomidine in ICU sedation.
- Study W97-245. A Phase III, multi-center, randomized, placebo-controlled double-blind study evaluating the safety and efficacy of dexmedetomidine when compared to placebo, with midazolam, for ICU sedation in post-operative patients.
- Study W97-246. A Phase III, multi-center, randomized, placebo-controlled, double-blind study evaluating the safety and efficacy of dexmedetomidine when compared to placebo, with propofol, for ICU sedation in post-operative patients.

Overall, these clinical studies demonstrated that dexmedetomidine was an effective sedative. It was safe and well tolerated in healthy patients, in post-operative patients requiring sedation in the ICU, and in mechanically ventilated patients requiring sedation in the ICU. The onset of the sedative effects of dexmedetomidine was rapid and the effect was consistently maintained throughout the duration of the infusions. Tolerance did not develop to the sedative effects during the infusion period. Study W97-249 also demonstrated that also possessed analgesic and anti-anxiety effects. Dexmedetomidine-treated patients required significantly less morphine and midazolam than placebo-treated patients. Consistent with its pharmacological profile, dexmedetomidine elicited dose-dependent decreases in heart rate and blood pressure. Somnolence and dry mouth were the most commonly reported adverse events that were possibly or probably related to dexmedetomidine. Four cases of dexmedetomidine overdoses were reported; all subjects recovered. Overdosage was observed when patients received twice to twenty-five times the prescribed dosage. Symptoms of dexmedetomidine overdose included: cardiac arrest, bradycardia, heart disorder, acidosis, and hyperkalemia.

*No cases of drug seeking behavior and the development of physical dependence were reported in these clinical trials. However, it must be emphasized that these clinical trials were not designed to address these issues.*

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**SUMMARY.**

\_\_\_\_\_ is an  $\alpha_2$  adrenergic agonist indicated for ICU sedation. \_\_\_\_\_ injectable solution will be available in one strength, 100 mcg/mL. \_\_\_\_\_ should be administered by a controlled infusion device. The dose is individualized and titrated to the desired clinical effect. In adult patients, it is recommended that the initial loading dose be 1.0 mcg/kg over 10 minutes, followed by a maintenance infusion of 0.2 to 0.7 mcg/kg/hr.

Preclinical abuse liability assessment of dexmedetomidine has demonstrated that it is psychoactive and that it has a dependence-producing potential equivalent to the opioid drug class. Dexmedetomidine functioned as a positive reinforcer in primates. Dexmedetomidine, at a dose of 1.0  $\mu$ g/kg, maintained self-administration behavior that was higher than those maintained by saline. The 0.0625  $\mu$ g/kg dose of dexmedetomidine did not maintain self-administration greater than saline in any of the monkeys. The 0.25  $\mu$ g/kg dose of dexmedetomidine maintained high rates of self-administration in one of the four monkeys tested. Pentazocine (125.0 and 250  $\mu$ g/kg) also functioned as a positive reinforcer in the monkeys tested with dexmedetomidine.

Dexmedetomidine was shown to have dependence-producing potential. Its dependence-potential was opioid-like in primates. As reported for clonidine (Katz, J., Psychopharmacology, 88:392-397, 1988), dexmedetomidine (8.0 and 16.0  $\mu$ g/kg) eliminated some but not all withdrawal signs that developed when morphine was withheld in morphine-dependent rhesus monkeys. A mild withdrawal syndrome was observed in rats that was infused with dexmedetomidine for 7 days. The withdrawal syndrome consisted of both behavioral and autonomic nervous system signs. These withdrawal signs included: loss in body weight, hyperirritability and diarrhea.

In conclusion, results from the preclinical studies reviewed have demonstrated that dexmedetomidine has an abuse liability profile similar to clonidine. Dexmedetomidine and clonidine (Woolverton, W., et al., Psychopharmacology, 77:17-23, 1982; Weerts, E.M., and Griffiths, R.R, Drug Alcohol Depend., 53:207-14, 1999) are both self-administered by monkeys, can suppress some of the withdrawal signs associated with morphine physical dependence and can produce physical dependence in rats. Based on these results, one can conclude that dexmedetomidine will have an abuse profile similar to that of clonidine; and therefore it should be subject to the same level of regulation. Cases of clonidine abuse by subjects with a history of substance abuse (Schaat, J., and et al., Am-J Psychiatry, 140:12625-1627, 1983; Lauzon, P., Journal of Substance Abuse Treatment, 9:125-127, 1992) and in subjects with no history of substance abuse (Sharma, A., and Newton, W., JABFP, 8:136-138, 1995; Agelink, A., et al., Nervenarzt, 67:253-255, 1996) have been published.

**LABELING REVIEW.**

The proposed draft labeling has been reviewed and the following changes are recommended:

**DRUG ABUSE AND DEPENDENCE:**

This section has been rewritten as follows:

\_\_\_\_\_ (dexmedetomidine hydrochloride) is not a controlled substance. However, \_\_\_\_\_ may produce a central nervous system profile, and withdrawal syndrome similar to that of clonidine.

**Humans.** The dependence potential of dexmedetomidine has not been studied in humans.

**Animals.** Studies in rodents and primates have shown that dexmedetomidine exhibits pharmacologic actions common to clonidine. In primate model to assess the positive reinforcing effects of psychoactive drugs, dexmedetomidine was self-administered intravenously. Dexmedetomidine produced opioid-like physical dependence; it substituted for morphine in morphine-dependent primates.

**RECOMMENDATIONS.**

*IL was in the  
pream to exam  
of the NDA -  
POLPNS -  
mod 5HT binding!*

The abuse liability assessment package infers, but does not establish with certainty, that dexmedetomidine has a potential for abuse. The abuse liability assessment package also did not include the receptor binding data, which is important in the evaluation. The dependence-producing potential of dexmedetomidine was opioid-like. It possesses cross-physical dependence potential for morphine which was less than that of codeine. Dexmedetomidine functioned as a positive reinforcer at doses lower than that of pentazocine. The submitted preclinical studies were largely descriptive and did not include some needed parameters. For instance, the following parameters were not described for the primate self-administration study: 1) The history (i.e., drugs, use in other self-administration and/or behavioral studies); 2) The training drug and dose; 3) Duration (i.e., limited or unlimited access) of the behavioral session; and 4) The FR value for drug delivery. The design of the primate physical dependence study was fairly consistent with the traditionally used paradigm with one exception; it is customary that each subject serves as his own control. In this study, saline was not tested in all the subjects. The goal of the physical dependence study in rats was to determine if dexmedetomidine will produce a withdrawal syndrome after long-term use; however the design of this study was not appropriate. Drug exposure for 3 or 7 days is not sufficient for the development of physical dependence. The induction period should had been for at least 2 to 3 weeks. No evidence of euphoria or drug-liking was seen in the submitted clinical studies. However, the clinical studies were not designed to characterize dexmedetomidine dependence-producing potential in humans.

(It is recommended that \_\_\_\_\_ not be scheduled under the CSA because there is a lack of data to support such a regulatory action. However, should other dosage forms of dexmedetomidine be submitted in new NDA's, the abuse potential would need to be reexamined especially in light of the possibility of more widespread use and availability. Minor labeling revisions are recommended prior to approval, refer to the suggested label changes recommended under the section title Labeling Review.

*? Reports of abuse to medical literature (1997 1997)*

*IS!*  
\_\_\_\_\_  
BeLinda A. Hayes, Ph.D. *July 24, 1999*  
Date

Concurred By Team Leader:

*IS!*  
\_\_\_\_\_  
Michael Klein, Ph.D. *July 29, 1999*  
Date

**APPEARS THIS WAY  
ON ORIGINAL**

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

FINAL SUMMARY OF CLINICAL INSPECTIONS

DATE: December 7, 1999

TO: Susmita Samanta, Regulatory Project Manager/HFD-170  
Patricia Hartwell, Clinical Reviewer/HFD-170  
Bob Rappaport, Medical Team-Leader/HFD-170  
Division of Anesthetics, Critical Care and Addiction Drug Products /HFD-170

THROUGH: Bette Barton, Ph.D., M.D., Chief  
Good Clinical Practice Branch I/HFD-46  
Division of Scientific Investigations 

FROM: Mary-Jo Zollo  
Good Clinical Practice Branch I/HFD-46  
Division of Scientific Investigations

SUBJECT: Final Summary of Clinical Inspections

NDA: NDA #21,038

APPLICANT: Abbott Laboratories

DRUG:            (Dexmedetomidine HCl)

CHEMICAL CLASSIFICATION: 1

THERAPEUTIC CLASSIFICATION: S

INDICATION: Alpha-2 sedative with analgesic properties indicated for use in an intensive care setting.

ACTION GOAL DATE: October 18, 1999

I. BACKGROUND:

The sites with the largest pool of subjects, for each of the 2 pivotal studies, were selected for data validation inspections. The sites/protocols inspected were:

1. Professor Dr. Eike Martin, F.A.N.Z.C.A. Protocol #W97-246  
Director of Anesthesiology  
University of Heidelberg  
Im Neuenheimer Feld 110  
69120 Heildeberg, Germany
2. Dr. R. M. Grounds Protocol #W97-245  
St. George's Hospital  
Consultant Anesthesia/Intensive Care  
Blackshaw Road  
Tootong SW17  
London SW17 ORE England

II. RESULTS

Both inspections have been completed. Both EIRs have been received and reviewed by Mary Jo Zollo/HFD-46.

1. Dr. Martin's study site. Protocol #W97-246

The records of all 45 subjects enrolled in this site for protocol #W97-246 were reviewed during the inspection. No significant discrepancies that would impact the study results were identified. The data from this study site appears acceptable.

2. Dr. Grounds' study site. Protocol #W97-245

The records of all 45 subjects enrolled in this site for protocol #W97-245 were reviewed during the inspection. The study site did not use appropriate practices for correcting data, however, the corrected data appeared to be of minimal clinical significance. DSI review of the EIR revealed that 5 of the 45 subjects (subjects #00103, #00104, #00105, 00106, and #00301) were enrolled into the study out of sequence (with either the screening date or the randomization date), and one of these five subjects (subject #00301) also appeared to be a seven year old child who did not meet study inclusion criteria (for age). DSI requested the clinical investigator to clarify the discrepancies.

A response was received from Dr. \_\_\_\_\_ concerning the above discrepancies. The 5 subjects that appeared to be enrolled into the study out of sequence with either the screening date or randomization date were entered into the study based upon scheduled surgery date (delay due to British National Health Service's procedure for scheduling elective surgery).

A transcription error occurred in recording the birth date of subject 00301. The subject was born on August 10, 1966 and was 31 years of age at time of entry to the study.

### III. RECOMMENDATIONS

DSI recommends that the data from these studies may be used to support drug claims. Follow-up action is not indicated.

Signature: \_\_\_\_\_  
GCPB Reviewer Name: Mary-Jo Zollo  
GCP-I/HFD-46

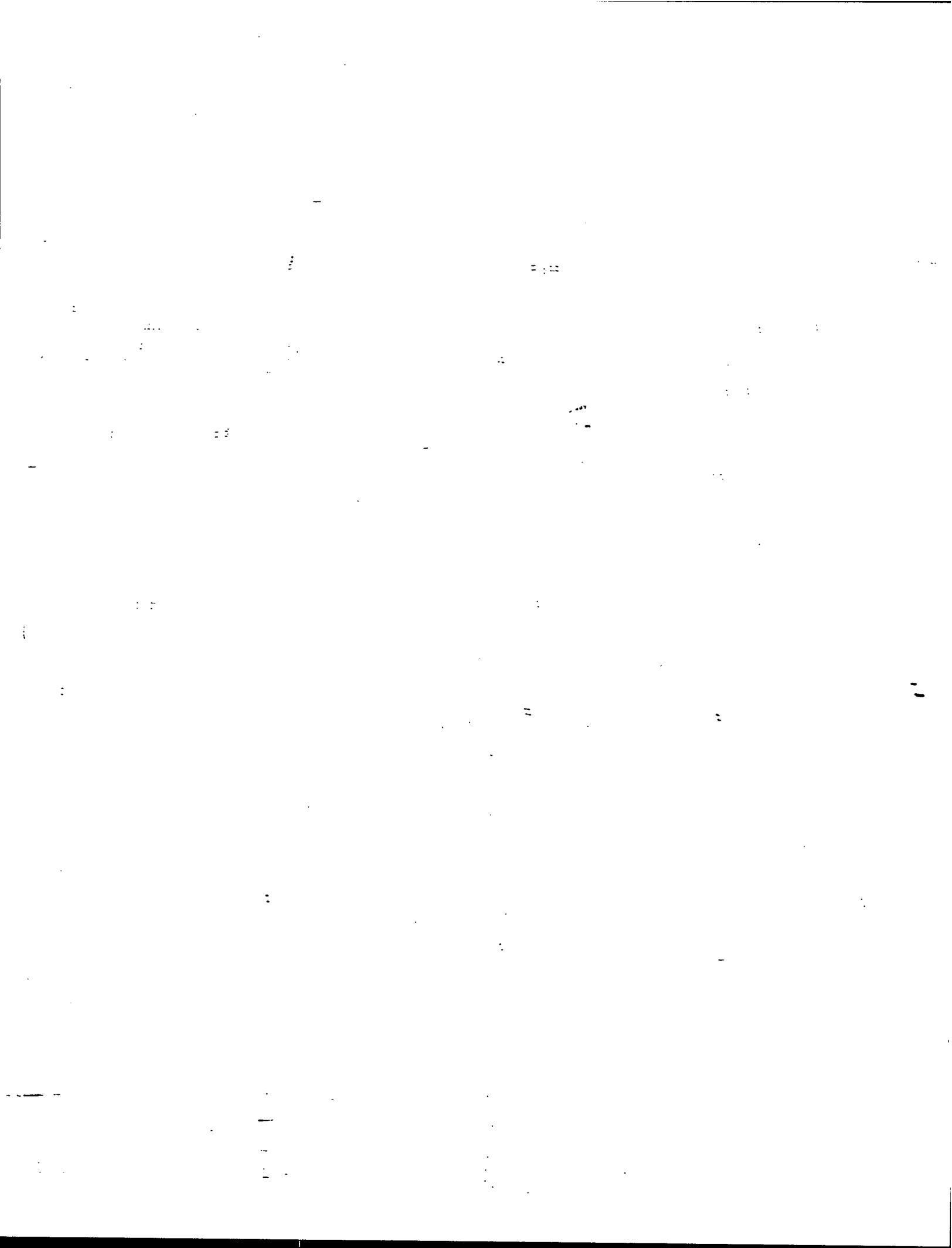
CONCURRENCE:

Supervisory comments

---

Bette Barton, Ph.D., M.D., Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations

**APPEARS THIS WAY  
ON ORIGINAL**





DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Rockville MD 20857

DEC 13 1999

Robert M. Grounds, M.D., FFARCS  
Consultant Anesthesia/Intensive Care  
St. Georges Hospital  
Blackshaw Road  
Tootong SW17  
London, England

Dear Dr. Grounds:

We have received your letter of October 5, 1999 in which you responded to our letter of September 21, 1999 regarding the clinical study (protocol #W97-245) of the investigational drug dexmedetomidine.

Your letter satisfactorily addresses our concerns and we accept your explanations. Your letter has been added to your file. If information is requested from your file in accord with the Freedom of Information Act, our response will include the related correspondence in your file; this serves to give a more complete picture.

Sincerely yours,

*ISI*  
Bette L. Barton, Ph.D., M.D.  
Chief, Good Clinical Practices Branch I, HFD-46  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Suite 125  
Rockville, MD 20855

Page 2 - Robert M. Grounds, M.D.

bcc:

HFA-224

HFD- Doc. Rm. NDA 20,733

HFD-170 Review Div. Dir.

HFD-170 MO

HFD-170 PM/CSO (Chite)

HFD-45/Reading File

HFD-46/Chron File

HFD-46/CIB File 9862

HFD-46/Zollo

HFD-47 Thomas

HFD-46 Prager

HFR-SW150 DIB

HFR-SW150 BIMO MONITOR

HFR-SW150 Beltran

HFC-134 Kadar

CFN: 96 - 1714

                      
drafted: MJZ: 11/29/99

final: nlp: 12/8/99

**APPEARS THIS WAY  
ON ORIGINAL**

# 372407  
MFA 21038  
YMR

CJ = 9862  
for MT/ncz

**Intensive Therapy Unit**  
**1st Floor St James Wing**



**Director.** E D Bennett FRCP.  
Professor of Intensive Care Medicine  
University of London

**Consultants.** J Allt-Graham BSc .FFARACS .FRCA.  
R M Grounds MD FRCA DA  
P J Newman MB, BS. FRCA  
A Rhodes MRCP, FRCA.

**St. George's Hospital**  
Blackshaw Road, London SW17 0QT  
Telephone: 0181-672 1255  
Fax:  
Ext:

5<sup>th</sup> October 1999

**Dr Bette Barton Ph.D, M.D. FCAP**  
**Good Clinical Practices Branch 1, HFD - 46**  
**Food and Drug Administration**  
**7520 Standish Place, Suite 125**  
**Rockville, MD 20855**  
**United States of America.**

Dear Dr Barton,

Thank you for your letter of 21 September.

With regard to your points 1 and 2 noting deviations from procedures required by Protocol W97-245.

1. The protocol in section 4.6 on Randomization does state that after written informed consent has been obtained and all screening criteria have been met, patients in the study will be assigned a study number and that the protocol requires patients to be assigned the next available patient number. However, the protocol allows for assessment and pre study screening to be conducted up to one week prior to initial dosing. (Physical Examination and Medical History Section 7.3.1.2). Thus some patients were seen and examined in the seven days prior to dosing. Written Informed Consent to participate in the study was obtained from these patients at that time. However, the British National Health Service (due to financial pressures) cannot always guarantee to perform Elective surgery on the proposed day and frequently patient's operation dates will be temporarily delayed. Consequently these patient's were allocated study numbers only after their scheduled surgery had been commenced because if their surgery had been postponed longer than seven days then the Physical examination and Medical History would need to be repeated. You will note from the records provided (and shown to Mr Beltran) that study number allocation for these patients was sequential for the date of their surgery.

2. You are correct protocol section 5.3.3. does state that patients should be over 18 years of age. Subject 00301 was in fact 31 years of age (date of birth 10 Aug 1966) at the time of entry to the study. I enclose a photocopy of our record of his date of birth at the screening visit. The date of birth 8 August 1990 was a transcription error from this original document to the Study Master File. This error in transcription had been noted and reported to Mr Beltran during his visit.

I hope this answers any questions you may have. If you have any more questions please do not hesitate to contact me at the above address.

Yours sincerely



R M Grounds LRCP, MRCS., MB, BS., MD., FRCA., DA(Eng.).  
Consultant in Anaesthesia and Intensive Care Medicine.

**APPEARS THIS WAY  
ON ORIGINAL**

**MEMORANDUM**

Date: April 14, 1999

To: David LePay, M.D., Director, DSI/HFD-340  
Mathew Thomas, M.D., CIB Reviewer/HFD-344

From: Cynthia G. McCormick, M.D., Director, Review Division/HFD-170  
David Morgan, Regulatory Project Manager, HFD-170

Subject: Request for Clinical Inspections for NDA 21-038

In support of the above mentioned NDA/Supplement for \_\_\_\_\_  
(dexmedetomidine HCl), the sponsor Abbott Laboratories has submitted the results of the  
following pivotal protocols for the indications identified below:

Indication	Pivotal Prot #	Investigator's Name/Address
Sedation ICU	W97-245	R.M. Grounds, M.D. St' George's Hospital. Department of Anesthesia Blackshaw Road London SW17 ORE England
Sedation ICU	W37-246	Eike Martin, M.D. Klinik f. Anaesthesiologie Universitätskliniken Im Neuenheimer Feld 110 69120 Heidelberg, Germany

We have discussed this application with Mathew Thomas and as a result identified the  
above protocols/sites for inspection.

(if applicable) We have requested the international inspections because (please check  
appropriate statements):

There are insufficient domestic data; (The sites selected contain the largest pool of  
subjects).

Only foreign data are submitted to support an application; or

Domestic and foreign data show conflicting results pertinent to decision-making;  
or

There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct,  
significant human subject protection violations.

NDA 21-038

Page 2

Other

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We request that the inspections be performed and the Inspection Summary Results be provided by September 1, 1999. We intend to make a regulatory decision on this application by October 17, 1999.

Should you require any additional information please contact, David Morgan, Regulatory Project Manager at 301-827-7410.

Concurrence:

Bob Rappaport, M.D.	Medical Team Leader
Charles Cortinovis, M.D.	Medical Reviewer

**APPEARS THIS WAY  
ON ORIGINAL**

Distribution: NDA 21-038  
HFD-170/Division File  
HFD-170/D.Morgan  
HFD-170/C.Moody  
HFD-344/M.Thomas

2000

Robert M. Grounds, M.D., FFARCS  
Consultant Anesthesia/Intensive Care  
St. Georges Hospital  
Blackshaw Road  
Tootong SW17  
London, England

2000 2 1 1999

Dear Dr. Grounds:

Between June 21 and June 24, 1999, Mr. David M. Beltran, representing the Food and Drug Administration (Agency) inspected your conduct as the investigator of record of a clinical study (protocol #W97-245) of the investigational drug dexmedetomidine. You conducted this study for Abbott Laboratories. This inspection is a part of the Agency's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

At the close of the inspection, Mr. Beltran discussed with you the importance of initialing and dating all corrections on documents. You stated that you would be more diligent in the future when making corrections to data entries.

From an evaluation of the inspection report and the Subject Screening/Enrollment Log collected during the inspection, we noted deviations from procedures required by Protocol #W97-245 that appear to be significant.

1. The protocol, in section 4.6 on Randomization, states that "after written informed consent has been obtained and all screening criteria have been met, patients in the study will be assigned a study number." Although the protocol requires patients to "be assigned the next available patient number," subject numbers 00103, 00104, 00105, 00106, and 00301 appear to have been assigned patient numbers out of sequence with the date screened and date enrolled.

2. The protocol, in section 5.3.3. on Inclusion Criteria, states the "patient is ... aged 18 years and over...." Subject number 00301 was 7 years old at the time of enrollment in the study (birth date August 8, 1990, enrollment date May 14, 1998).

recovery  
of patients  
DL

**BEST POSSIBLE COPY**

# BEST POSSIBLE COPY

If you would like to provide a written response and/or supporting documentation to clarify the matters discussed above, mail it to:

Dr. Bette Barton Ph.D, M.D. FCAP  
Good Clinical Practices Branch I, HFD-46  
Food and Drug Administration  
7520 Standish Place, Suite 125  
Rockville, MD 20855  
United States of America

Please make appropriate corrections/changes in your procedures to assure the findings noted above are not repeated in any of your ongoing or future studies.

We appreciate the cooperation shown Mr. Beltran during the inspection.

Sincerely yours,

  
Bette L. Barton, Ph.D., M.D.  
Chief  
Good Clinical Practices Branch I  
Division of Scientific Investigations, HFD-46  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place  
Suite 125  
Rockville, MD 20855

**APPEARS THIS WAY  
ON ORIGINAL**

.cc:

HFA-224  
HFD- Doc. Rm. NDA 20,733  
HFD-170 Review Div.Dir.  
HFD-170 MO  
HFD-170 PM/CSO (Chite)  
HFD-45/Reading File  
HFD-46/Chron File  
HFD-46/CIB File  
HFD-46/Zollo  
HFD-47 Thomas  
HFD-46 Prager  
HFR-SW150 DIB  
HFR-SW150 BIMO MONITOR  
HFR-SW150 Beltran  
HFC-134 Kadar

CFN: 96 - 1714

Field Classification: NAI

Headquarters Classification:

<input type="checkbox"/> 1)NAI	
<input type="checkbox"/> 2)VAI	no response required
<input checked="" type="checkbox"/> 3)VAI-R	response requested
<input type="checkbox"/> 4)VAI-RR	adequate response received prior to issuance of VAI-R letter
<input type="checkbox"/> 5)OAI	

If the Field and Headquarters classifications are different, explain why: HFD-46 review found protocol violations not noted during inspection.

Deficiencies noted:

<input type="checkbox"/>	inadequate consent form
<input type="checkbox"/>	inadequate drug accountability
<input checked="" type="checkbox"/>	deviations from protocol
<input type="checkbox"/>	inadequate records
<input type="checkbox"/>	failure to report ADRs
<input type="checkbox"/>	other (specify)

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drafted: MJZ:09/07/99

reviewed: BLE:09/14/99

revised: MJZ:09/14/99

Note to Review Division and DSI Recommendation:

The field investigator audited 45 of the 45 subjects enrolled in protocol. Problems with document corrections not being initialed and dated were noted during the inspection. DSI review also found a problem with 5 of the 42 subjects entered into the study out of sequence with either the screening date or enrollment date and one subject not meeting the inclusion criteria for age. DSI recommend that the data for subject numbers 00103, 00104, 00105, 00105, and 00301 not be used in support of the NDA,

APPEARS THIS WAY  
ON ORIGINAL

*M. Connick*

Food and Drug Administration  
Rockville MD 20857

SEP 21 1999

Professor Dr. Eike Martin, F.A.N.Z.C.A.  
Director, Anesthesiology  
University of Heidelberg  
Im Neuenheimer Feld 110  
69120 Heidelberg, Germany

Dear Dr. Martin:

The purpose of this letter is to inform you of our conclusions concerning your conduct of the clinical study (protocol # W97-246 ) of dexmedetomidine that you conducted for Abbott Laboratories.

From June 14 to June 17, 1999, Mr. David M. Beltran and Dr. Mathew Thomas, representing the Food and Drug Administration (Agency), inspected the study identified above. At the close of the inspection, Mr. Beltran and Dr. Thomas provided you their inspectional observations (i.e., Form FDA 483) and discussed these observations with you. We reviewed (a) the inspection report, (b) the documents copied during the inspection, (c) your oral responses during the inspection to the inspectional observations, and (d) your letter of July 9, 1999 that you addressed to Dr. Thomas and in which you responded to the inspectional observations.

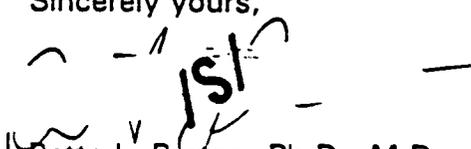
Your letter of July 9, 1999, responds to the items listed on the Form FDA 483 and satisfactorily addresses our concerns. Your letter has been added to your file. If information is requested from your file in accord with the Freedom of Information Act, our response will include the related correspondence in your file; this serves to give a more complete picture.

This inspection is part of the Agency's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected. We appreciate the cooperations shown Mr. Beltran and Dr. Thomas during the inspection.

Page 2 - Professor Dr. Eike Martin, F.A.N.Z.C.A

Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

  
Bette L. Barton, Ph.D., M.D.

Chief

Good Clinical Practices Branch I, HFD-46  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Suite 125  
Rockville, MD 20855

**APPEARS THIS WAY  
ON ORIGINAL**

cc:

HFA-224

HFD-170 Doc. Rm. NDA 21,038

HFD-170 Review Div. Dir.

HFD-170 MO

HFD-170 PM/CSO

HFD-45/Reading File

HFD-46/Chron File

HFD-46/CIB File 9851

HFD-46/Zollo

HFR-SW150 DIB

HFR-SW150 BIMONITOR

HFR-SW150(Betran)

HFC-134 Kadar

CFN: 96-17640

Field Classification:

Headquarters Classification:

1)NAI

2)VAI no response required

3)VAI-R response requested

4)VAI-RR adequate response received prior to issuance of VAI-R letter

5)OAI-WL warning letter

6)OAI-NIDPOE

If the Field and Headquarters classifications are different, explain why:

Deficiencies noted:

inadequate consent form

inadequate drug accountability

deviations from protocol

inadequate records

failure to report ADRs

other (specify)

drafted: MJZ:09/09/99

reviewed: BLB:09/14/99

revised: MJZ:09/14/99

Note to Review Division and DSI Recommendation:

The field investigator audited 45 of the 45 subjects enrolled in protocol. The data appear acceptable for use in support of drug claims.

**APPEARS THIS WAY  
ON ORIGINAL**