

- One patient experienced a myocardial infarction said to have unlikely causality.

### PHASE III STUDIES

Deaths:

None

Serious Adverse Events:

- Patient experienced hypotension probably related to study drug; dyspnea/chest pain and pneumothorax with no stated relationship to study drug.
- Patient experienced cardiac arrest with a claimed possible relationship to study drug.
- Patient experienced diarrhea, tissue discharge, necrotic area on buttock, ischemic colitis, and vaginal fistula with claimed no relationship to study drug. Both the diarrhea and necrotic area on buttock were judged to be mild while the tissue discharge, ischemic colitis, and vaginal fistula were judged to be moderate.

## **SECTION 8.7 LABORATORY FINDINGS**

### **SECTION 8.7.1 SERUM CHEMISTRY PARAMETERS**

A summary of mean change from baseline to the last post baseline time point in hematology and chemistry parameters for patients in Phase II/III continuous infusion studies is presented in Table 41. Sponsor states the mean changes from baseline in hematology and chemistry values appear consistent with what would be expected in this post-surgical population. Statistically significant differences were noted between the randomized Dexmedetomidine treated patients and placebo treated patients for mean changes from baseline hematocrit, hemoglobin, and red blood cells. These changes are claimed by the sponsor to be small and not clinically important. This reviewer agrees that these hematology changes are small and not clinically insignificant.

Adverse events of hyperglycemia were reported by 2% of the patients in both the randomized Dexmedetomidine and placebo treatment groups but the mean change from baseline to the last post baseline time point in glucose values were statistically significantly higher in the randomized Dexmedetomidine patients than in the placebo patients. The changes were 1.5 mmol/L increase for randomized Dexmedetomidine patients and 1.0 mmol/L increase for placebo patients. [*Reviewer Note: Normal fasting glucose is 4.2-6.4 mmol/L or 75-115 mg/dL.*] Urine glucose was not collected in the Dexmedetomidine studies.

The mean changes from baseline to the last post baseline time point in liver chemistry parameters were similar between randomized Dexmedetomidine and placebo patients.

Table 41 Mean Change From Baseline to the Last Post Baseline Time Point in Hematology And Chemistry Parameters: All Treated Patients in Phase II/III Continuous Infusion Studies.

	All Treated Dexmedetomidine			Randomized Dexmedetomidine			Placebo		
	N	Base ±SD	Mean Change ±SD	N	Base ±SD	Mean Change ±SD	N	Base ±SD	Mean Change ±SD
<b>Hematology Parameter</b>									
Hematocrit (L/L)	1046	0.4 ±0.07	0.0 ±0.07	915	0.4 ±0.07	-0.1* ±0.07	641	0.4 ±0.07	0.0 ±0.07
Hemoglobin (g/L)	1077	121.5 ± 22.23	-16.1 ± 22.87	936	123.2 ± 22.04	-17.6* ± 23.13	673	121.3 ± 22.54	-16.6 ± 23.87
Platelets (x10 <sup>9</sup> /L)	947	227.0 ±92.94	-36.9 ± 58.36	832	230.4 ± 92.69	-39.2 58.83	579	226.1 ± 90.20	-36.7 ±60.63
RBC (x 10 <sup>12</sup> /L)	673	3.8 ±0.72	-0.3 ± 0.72	533	3.9 ±0.74	-0.3* ±0.75	469	3.8 ±0.72	-0.3 ±0.74
WBC (x10 <sup>9</sup> /L)	1075	8.1 ±3.56	3.4 ± 3.94	934	7.9 ±3.33	3.5 ±3.87	666	8.1 ± 3.28	3.4 ±3.79
<b>Chemistry Parameter</b>									
BUN/Urea (mmol/L)	1131	5.3 ±2.10	-0.1 ±2.55	976	5.3 ±2.12	-0.2 ±2.47	706	5.6 ± 2.58	-0.1 ± 2.59
Bicarbonate (mmol/L)	1091	23.9 ± 3.54	1.4 ±3.55	942	24.2 ± 3.56	1.3 ±3.60	685	23.6 ± 3.55	1.6 ± 3.63
Creatinine (umol/L)	1127	77.6 ±27.75	1.8 ±35.17	971	78.9 ±27.19	1.1 ±34.89	708	76.7 ±29.53	3.1 ±26.81
Glucose (mmol/L)	1094	7.0 ±2.70	1.3 ±4.52	946	6.9 ±2.62	1.5* ±4.25	688	7.2 ±2.78	1.0 ±3.42
LDH (U/L)	598	242.0 ± 135.52	56.0 ±197.27	598	242.0 ±135.52	56.0 ±197.27	358	234.7 ±150.82	57.7 ±177.44
Potassium (mmol/L)	1104	4.2 ± 0.46	-0.1 ±0.60	952	4.2 ±0.46	-0.1 ±0.59	696	4.2 ±0.45	-0.1 ±0.57
SGOT/ASAT (U/L)	1082	28.4 ± 43.70	8.9 ±61.30	933	26.7 ± 31.62	10.0 ±58.88	683	30.0 ± 82.47	6.4 ± 77.32
SGPT/ALAT (U/L)	1067	24.6 ± 37.52	4.4 ±74.93	918	24.4 ± 36.02	3.5 ±78.06	672	24.6 ± 46.89	3.8 ± 43.58
Total bilirubin (umol/L)	1056	11.3 ± 10.17	1.1 ±8.02	907	11.0 ± 10.39	1.6 ±7.92	665	12.2 ± 11.48	1.1 ± 10.04
Total protein (g/L)	1083	59.5 ± 13.3	-6.6 ±12.68	927	61.0 ±13.05	-7.8 ±12.40	684	59.1 ±13.61	-5.6 ± 12.65

Modified Sponsor's Table 33 ISS Vol 8/10-239-83

N = number of patients; base = baseline; SD = standard deviation; RBC = red blood cells;  
WBC = white blood cells;

BUN = blood urea nitrogen; LDH= lactate dehydrogenase; SGOT/ASAT = serum  
glutamic oxaloacetic transaminase/aspartate transaminase; SGPT/ALAT = serum  
glutamic-pyruvic transaminase/alanine transaminase

\* Statistically significant difference (Shaded Areas) between randomized  
dexmedetomidine patients and placebo patients,  $p \leq 0.05$ .

## SECTION 8.7.2 VITAL SIGNS AND ELECTROCARDIOGRAMS

### Phase I Studies

One of the Phase I studies was designed to determine the highest safe plasma concentrations of Dexmedetomidine. Continuous monitoring of subjects EKGs was performed. The Dexmedetomidine plasma concentrations achieved were greater than those expected based on PK parameters in use. A total of 7 subjects in the study had significant abnormalities on post-baseline EKGs; all had received Dexmedetomidine. 5 subjects had sinus bradycardia; one also had nonsustained junctional rhythm. One subject had Mobitz Type I second degree heart block which resolved spontaneously one minute after onset. Another subject had intermittent premature atrial contractions with variable first degree AV block.

The EKG disorders occurred primarily at the plasma concentrations  $> 1.2$  ng/ml. Sponsor speculates the probable mechanism of action was enhanced vagal nerve reflex activity without opposing sympathetic activity. Evaluation was confounded by use of phenylephrine which was used to determine baroreceptor sensitivity. Known adverse effects of phenylephrine administration include bradycardia and heart block. In this study involving EKGs, subjects were able to tolerate Dexmedetomidine plasma concentrations exceeding the anticipated therapeutic range by as much as 13 times.

#### Phase II/III Studies

Several of the perioperative studies collected vital sign data using a said novel monitoring system. Sponsor claims that as a result of validation concerns about the system and the inability to synchronize the data with an actual event or time of treatment, the data collected by this system could not be appropriately analyzed or interpreted. The vital sign data collected in the Phase II/III ICU sedation studies used traditional techniques to assure the reliability of the data. Because of the validation concerns, sponsor is only presenting vital sign data from the continuous infusion ICU sedation studies in the Integrated Summary of Safety.

Analyses of vital signs in the continuous infusion ICU sedation studies included systolic and diastolic blood pressure, heart rate, central venous pressure, respiratory rate, oxygen saturation, and cardiac output.

#### Systolic Blood Pressure (SBP):

Mean baseline SBP was 126 mmHg in the randomized Dexmedetomidine group and 126 mmHg in the placebo group and was maintained within the normal range for both groups during the entire period of observation. After initial increases during the first 10 minutes, rapid moderate decreases (about 15 mmHg) occurred within the next 10 minutes in the randomized Dexmedetomidine group after which decreases occurred more gradually until 12-13 hours. After 15 hours, the time at which most patients completed study drug infusion, SBP slowly increased. In the placebo group, increases occurred during the first hour, after which there were decreases until 5 hours. Mean change from baseline in SBP during study drug infusion showed statistically significant differences between the treatment groups from 20 minutes through the 21 hour time point; variability between treatment and placebo groups was the same. After the 12-15 hour time point, SBP tended

to return to baseline with increases in the Dexmedetomidine group and decreases in the placebo group.

Randomized Dexmedetomidine patients with hypotension showed a mean decrease in SBP of 20 to 25 mmHg during the first 20 minutes. SBP in the randomized Dexmedetomidine group with hypotension remained lower than the randomized Dexmedetomidine group without hypotension until 17-hours, after which they were similar.

#### Diastolic Blood Pressure (DBP)

Baseline DBP was 64 mmHg in the placebo group and 65 in the randomized Dexmedetomidine group. In the randomized Dexmedetomidine group, after initial increases the first 10 minutes, DBP returned to baseline followed by gradual decreases to 12-13 hours and slight increases thereafter. In the placebo group, DBP remained increased for 2 hours before returning to baseline. At all times after the initial 10 minute evaluation, mean DBP was lower for the randomized Dexmedetomidine patients than for placebo patients. Analyses of mean change from baseline in DBP during study drug infusion showed statistically significant differences between the treatment groups at several time points. The most pronounced difference was at 12 hours after start of infusion with a difference of about 8 mmHg. Although statistically significant, the difference in variability between treated and placebo groups was clinically insignificant. Actual DBP was similar in the 2 groups by 24 to 27 hours.

#### Heart Rate

Baseline heart rate was 81 in the placebo group and 80 in the randomized Dexmedetomidine group. For the Dexmedetomidine treated group, heart rate decreased about 5 beats per minutes about 10 minutes after drug initiation. For both groups, mean rate remained within the normal range throughout the entire range of observation.

#### Central Venous Pressure (CVP)

Baseline CVP was 8 mmHg in the placebo group and 7 mmHg in the randomized Dexmedetomidine group. Mean change from baseline in CVP during study drug infusion showed small statistically significant differences between treatment groups from 1-12 hours, the differences were not clinically significant. Mean CVP for randomized Dexmedetomidine patients with hypotension was clinically insignificantly higher than in Dexmedetomidine patients without hypotension.

#### Respiratory Rate (RR)

Respiratory Rate was similar between treatment groups.

#### Oxygen Saturation

All patients received oxygen while being ventilated and remained in the normal range. After extubation oxygen saturation decreased slightly within both treatment groups but remained within the normal range. Oxygen saturation was similar between placebo and Dexmedetomidine treatment groups.

#### Cardiac Output

Few patients had cardiac output measurements collected during the study. Among those that did, the pattern of changes was similar between placebo and Dexmedetomidine treatment groups.

### SECTION 8.8 ADVERSE EVENTS AND PRECLINICAL STUDIES

In 28 day repeated dosing nonclinical toxicology studies, the primary Dexmedetomidine related effects were sedation, slightly reduced body weight, exophthalmos, piloerection, gait changes, muscle twitching, irregular respiration, glucosuria. *[Discussion with pharmacology reviewer Dr. Geyer discloses no concomitant elevations of blood glucose in the animals with glucosuria. However other animals in other studies did show significant hyperglycemia although the urine for glucose was not analyzed.]* Changes in hepatic weight, some hepatic serum enzymes, and pulmonary hemosiderin deposits were also observed at the highest doses studied. In the clinical studies, the most frequently reported adverse events were likely extensions of the pharmacological effects of alpha2 agonists, including hypotension, hypertension, and bradycardia.

A dose related increase in the incidence of corneal keratitis and opacities was also reported in the preclinical studies. Sponsor states these last ophthalmological findings were due to the pharmacological effect of Dexmedetomidine decreasing lacrimal secretions and blinking during sedation. *[This reviewer agrees with this assessment.]* A total of 8 patients in the Phase II/III continuous infusion studies reported vision disorders, including 5 reports of abnormal vision, one report of conjunctivitis, one report of diplopia, and one report of photopsia. The abnormal vision reports were primarily described as blurred vision. The one report of conjunctivitis was related to a corneal abrasion. Each of these events resolved without intervention.

### SECTION 8.9 DOSE-RESPONSE DATA

Sponsor states that one of the Phase I studies (Dexmedetomidine-95-007) demonstrated that subjects were able to tolerate Dexmedetomidine plasma concentrations exceeding the anticipated therapeutic range of 1.2 ng/ml; maximum individual Dexmedetomidine concentrations in this study ranged from 2.123 ng/ml to 16.100 ng/ml. A summary of the

most commonly experienced treatment emergent adverse events in Phase I continuous infusion studies by target plasma concentration is presented in Table 42.

Table 42 Most Common<sup>a</sup> Treatment Emergent Adverse Events By Target Dexmedetomidine Plasma Concentration:  
All Dexmedetomidine Treated Subjects  
Phase I Continuous Infusion Studies

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

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

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

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

Dex = Dexmedetomidine Concs = concentrations

In the Phase I continuous infusion studies, the incidence of dry mouth and somnolence was highest at the highest Dexmedetomidine plasma concentrations (75% and 83% respectively). However only 12 patients were dosed in this group. Sponsor states the incidence of somnolence showed no clear trend when analyzed by target plasma

concentration probably because some investigators considered somnolence an expected effect of the drug and did not report it as an adverse event.

A summary of the most commonly experienced treatment emergent adverse events in Phase II/III continuous infusion studies by total Dexmedetomidine dose is presented in Table 43.

Table 43 Most Common<sup>a</sup> Treatment Emergent Adverse Events by Total Dose of Dexmedetomidine: All Treated patients in Phase II/III Continuous Infusion Studies

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

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

NOS = not otherwise specified

a: Experienced by  $\geq 2\%$  of all Dexmedetomidine treated patients in Phase II/III continuous infusion studies

In the Phase II/III continuous infusion studies, evaluation of adverse events by total dose of Dexmedetomidine showed no obvious dose response relationship. The most common adverse event at all doses was hypotension. Hypertension was the next most commonly occurring adverse event although there was no apparent dose response relationship. Dry mouth did appear to demonstrate a dose-response relationship above the lower doses. Sponsor states the relatively high incidence of hypoxia (22%) in the 0-1 mcg/kg group can be attributed to the results of one study (Dexmedetomidine-96-012) where hypoxia was reported by  $\geq 75\%$  of patients in all treatment groups including patients receiving placebo. With respect to laboratory evaluations, examination of the mean change from baseline in hematology and chemistry parameters by total dose of Dexmedetomidine did not show any apparent dose-response relationship.

## SECTION 8.10 DRUG-DRUG INTERACTIONS

Potential drug interactions were assessed in six Phase I studies which evaluated the use of Dexmedetomidine with esmolol, alfentanil, isoflurane, midazolam, propofol and rocuronium. Adverse events were analyzed for patients who received midazolam or propofol in the Phase II/III sedation studies.

### Phase I Studies

#### Esmolol

One Phase I continuous infusion study evaluated Dexmedetomidine and esmolol and placebo and esmolol. The most commonly reported treatment emergent adverse event in this study was headache, with similar numbers of subjects reporting this event in the two dose groups. No other safety concerns were identified.

#### Alfentanil

One Phase I continuous infusion study evaluated Dexmedetomidine with alfentanil (N=10) compared to placebo with alfentanil (N=9). Subjects who received Dexmedetomidine and alfentanil had more reports of dry mouth (100% vs 56%), apnea (60 vs 11%), xerophthalmia (50% vs 11%), bradycardia (40% vs 0), and hypotension (40% vs 0). Apnea lasting less than 1 minute was reported in 6 Dexmedetomidine subjects vs 1 alfentanil-placebo subject.

#### Isoflurane

One Phase I continuous infusion study evaluated Dexmedetomidine-isoflurane (N=10) and placebo-isoflurane (N=9). Subjects who received Dexmedetomidine-isoflurane had more reports of hypotension (50% vs 0) and involuntary muscle contractions (50% vs 0) than the placebo-isoflurane group. Sponsor does not speculate on the etiology of the involuntary muscle contractions in the Dexmedetomidine-isoflurane group and claims the overall incidence of involuntary muscle contractions among all Dexmedetomidine treated patients in the Phase II/III continuous infusion studies was <1%.

#### Midazolam

One Phase I continuous infusion study evaluated Dexmedetomidine-midazolam (N=19) and placebo-midazolam (N=18). Somnolence (100% vs 11%), hypotension (95% vs 22%), and dry mouth (42% vs 0) were more common among the Dexmedetomidine-midazolam group than the placebo-midazolam group. No obvious safety concerns were identified when the Dexmedetomidine-propofol (N=10) group was compared to the placebo-propofol (N=9) patients.

#### Rocuronium

No adverse events were reported for subjects who received rocuronium and Dexmedetomidine (N=10).

### Phase II/III Studies

The investigation of potential interactions of Dexmedetomidine with midazolam or propofol was evaluated in Phase II/III continuous infusion ICU studies as presented in Table 44.

Table 44. Most Common Treatment Adverse Events by Drug Interaction in Phase II/III Continuous Infusion ICU Sedation Studies Experienced by  $\geq 2\%$  of Dexmedetomidine Treated Patients

Randomized Dexmedetomidine			Placebo		
Dexmedetomidine Only N=158	Dexmedetomidine And Midazolam N=104	Dexmedetomidine And propofol N=125	Placebo Only N=71	Placebo And Midazolam N=150	Placebo And Propofol N=158

Modified Sponsor's Table 48 ISS Vol 8/10-239-143

The proportion of patients experiencing hypertension or hypotension was higher in any group that included Dexmedetomidine as compared to any of the placebo groups. The proportion of patients who experienced bradycardia was higher among patients in the group who received Dexmedetomidine-propofol compared with patients in the groups who received Dexmedetomidine alone, Dexmedetomidine-midazolam, and placebo-propofol. Sponsor states that as propofol is known to produce bradycardia, Dexmedetomidine may have had an additive effect. Tests of significance were not noted in the comparisons of Drug Interactions in the Phase II/III Continuous Infusion Sedation Studies.

## **SECTION 8.11 DRUG-DEMOGRAPHIC INTERACTIONS**

Adverse events for the Phase II/III continuous infusion and the Phase II/III continuous infusion ICU sedation studies were analyzed to assess the potential effects of demographic characteristics including age and gender. The majority of the patients enrolled in these studies were Caucasian, precluding meaningful comparisons by ethnic origin.

### **AGE**

Randomized Dexmedetomidine treated patients in the 36 to 55 year old age group had a higher number of reports of hypotension compared to placebo treated patients in this age group. Randomized Dexmedetomidine exposed patients in the 56 to 65 year old age group had a higher number of reports of hypotension and bradycardia compared to placebo treated patients in this age group. Randomized Dexmedetomidine treated patients in the >65 year old age group had a higher number of reports of hypotension and bradycardia compared to placebo treated patients. Mean changes from baseline to the last post baseline time point for hematology and chemistry values were analyzed by age

group. While there were some statistically significant differences between some age groups, there does not appear to be any clinically meaningful trends in the analyses.

Table 45 Summary of Most Common<sup>a</sup> Treatment Emergent Adverse Events By Age Randomized Patients in Phase II/III Continuous Infusion Studies

Adverse Event	Randomized Dexmedetomidine			
	18 - 35 years (N=43)	36 - 55 years (N=297)	56 - 65 years (N=350)	> 65 years (N=458)
Patients with at least one treatment-emergent adverse event	24(56%)	187(63%)	196(56%)	289(63/6)
Hypotension	12(28%)	82 (28%)*	109 (31%)*	140 (31%)*
Hypertension	3(7%)	44(15%)	41 (12%)*	67(15%)
Nausea	6(14%)	50(17%)	37(11%)	53 (12%)
Bradycardia	3(7%)	13(4%)	22 (6%)*	41 (9%)*
Tachycardia	6(14%)	21(7%)	17(5%)	16(3%)
Fever	1 (2%)	23(8%)	12 (3%)*	20(4%)
Hypoxia	5(12%)	22(7%)	12(3%)	15 (3%)
Anemia	1(2%)	14(5%)	11(3%)	18(4%)
Vomiting	1(2%)	9(3%)	8(2%)	23(5%)
Hemorrhage NOS	1(2%)	7(2%)	8(2%)	15 (3%)
Pain	1(2%)	3 (1%)*	11(3%)	10(2%)
Rigors	0	4 (1%)*	6(2%)	20(4%)
Atrial fibrillation	0	4(1%)	8(2%)	15 (3%)
Mouth dry	0	5(2%)	3 (<1%)	9(2%)
Agitation	0	11(4%)	6 (2%)	11(2%)
Adverse Event	Placebo			
	18 - 35 years (N=34)	36-55 years (N=196)	56 - 65 years, (N=212)	> 65 Years (N=375)
Patients with at least one treatment-emergent adverse event	22(65%)	112(57%)	126(59%)	217(58%)
Hypotension	4(12%)	38(19%)	40(19%)	49 (13%)
Hypertension	4(12%)	28(14%)	39(18%)	64(17%)
Nausea	9(26%)	22(11%)	26(12%)	48(13%)
Bradycardia	2(6%)	4(2%)	5 (2%)	14(4%)
Tachycardia	2(6%)	24(12%)	17(8%)	19(5%)
Fever	3(9%)	12(6%)	19(9%)	8(2%)
Hypoxia	2(6%)	12(6%)	8(4%)	14(4%)
Anemia	1(3%)	6(3%)	9(4%)	8 (2%)
Vomiting	3(9%)	8(4%)	11 (5%)	21 (6%)
Hemorrhage NOS	2(6%)	5 (3%)	4(2%)	11 (3%)
Pain	1(3%)	7(4%)	4(2%)	7(2%)
Rigors	0	9(5%)	8(4%)	10(3%)
Atrial fibrillation	0	0	4(2%)	15(4%)
Mouth dry	0	0	1 (<1%)	3 (<1%)
Agitation	0	3(2%)	8(4%)	16(4%)

Sponsor's Table 49 ISS 8/10-239-145

NOS = not otherwise specified

a: Experienced by  $\geq 2\%$  of all dexmedetomidine-treated patients in Phase II/III continuous infusion studies

\* Statistically significant difference between randomized dexmedetomidine patients and placebo patients.

## GENDER

Randomized Dexmedetomidine treated patients who were male had a higher number of reports of hypotension and bradycardia compared to placebo treated patients who were male. Randomized Dexmedetomidine treated patients who were female had a higher number of reports of hypotension compared to placebo treated patients who were female.

Table 46 Summary of Most Common<sup>a</sup> Treatment Emergent Adverse Events By Gender: Randomized Patients in Phase II/III Continuous Infusion Studies

Adverse Event	Randomized Dexmedetomidine		Placebo	
	Male (N=790)	Female (N=358)	Male (N=555)	Female (N=262)
Patients with at least one treatment-emergent adverse event	486(62%)	209(58%)	318(57%)	159(61%)
Hypotension	259 (33%)*	84 (23%)*	91(16%)	40(15%)
Hypertension	112(14%)	43 (12%)	90(16%)	45(17%)
Nausea	70(9%)	76(21%)	50(9%)	55 (21%)
Bradycardia	63 (8%)*	16(4%)	20(4%)	5 (2%)
Tachycardia	45(6%)	15 (4%)*	39(7%)	23 (9%)
Fever	47(6%)	9(3%)	32(6%)	10(4%)
Hypoxia	30(4%)	24(7%)	22(4%)	14(5%)
Anemia	33 (4%)	11(3%)	15 (3%)	9(3%)
Vomiting	17(2%)	24(7%)	15 (3%)	28(11%)
Hemorrhage NOS	21(3%)	170 (3%)	16(3%)	6(2%)
Pain	21(3%)	4(1%)	11(2%)	8(3%)
Rigors	27(3%)	3 (<1%)	24(4%)	3 (1%)
Atrial fibrillation	25(3%)	2 (<1%)	15 (3%)	4(2%)
Mouth dry	12(2%)	5 (1%)	1 (<1%)	3 (1%)
Agitation	23 (3%)	5 (1%)	21(4%)	6(2%)

Sponsor's Table 50, ISS 8/10-239-147

NOS = not otherwise specified

a: Experienced by  $\geq 2\%$  of all Dexmedetomidine treated patients in Phase II/III continuous infusion studies

\* Statistically significant difference between randomized dexmedetomidine patients and placebo patients.

## DRUG-DISEASE INTERACTIONS:

Renal/Hepatic Failure:

Based on Phase I studies in renal and hepatic failure, sponsor makes the following statements:

In renally impaired subjects, Dexmedetomidine pharmacokinetics were not different compared to healthy subjects. Administration of Dexmedetomidine was well tolerated in the renally impaired subjects participating in the trial. In hepatically impaired subjects, the mean half life for the subjects with mild, moderate, and severe hepatic impairment was prolonged to 3.9, 5.4, and 7.4 hours, respectively, compared to subjects with normal hepatic function (2.5 hours). Consequently the dose of Dexmedetomidine may need to be reduced in subjects with hepatic impairment. A higher incidence of treatment emergent adverse events were reported among hepatically impaired subjects, including dry mouth, hypotension, and headache, compared with healthy subjects.

**Surgical Procedures:**

Adverse events for the Phase II/III continuous infusion ICU sedation studies were analyzed to assess the potential effects of the surgical procedures performed.

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ON ORIGINAL**

Table 47 Most Common<sup>a</sup> Treatment Emergent Adverse Events by Surgery Type:  
Randomized Patients in Phase II/III Continuous Infusion ICU Studies

Adverse Event	Randomized Dexmedetomidine			
	Head and Neck (N=27)	Cardiac (N=202)	Laparotomy (N=95)	Other (N=63)
Patients with at least one treatment-emergent adverse event	17(63%)	144(71%)	56(59%)	42(67%)
Hypotension	5 (19%)*	58 (29%)*	23 (24%)*	22 (35%)*
Hypertension	8(30%)	31(15%)	13(14%)	11(17%)
Nausea	1(4%)	31(15%)	8(8%)	2(3%)
Bradycardia	3 (11%)*	11(5%)	3(3%)	10 (16%)*
Mouth dry	1(4%)	11(5%)	1 (1%)	0
Fever	4(15%)	2 (<1%)	4(4%)	8(13%)
Vomiting	1(4%)	11 (5%)	4(4%)	0
Atrial fibrillation	1(4%)	13(6%)	1 (1%)	1(2%)
Hypoxia	1(4%)	12(6%)	1 (1%)	2(3%)
Anemia	2(7%)	3(1%)	4(4%)	2(3%)
Pain	0	7(3%)	0	2(3%)
Tachycardia	2(7%)	3(1%)	3(3%)	4(6%)
Hemorrhage not otherwise specified (NOS)	0	9(4%)	2(2%)	1(2%)
Pleural effusion	0	6(3%)	2(2%)	0
Hypovolemia	1(4%)	2 (<1%)	1 (1%)	1(2%)
Thirst	0	5 (2%)	0	3 (5%)
Rigors	2(7%)	1 (<1%)*	4(4%)	1(2%)
Hyperpyrexia	0	1 (<1%)	5 (5%)	1(2%)
Agitation	2(7%)	2 (<1%)	3(3%)	1(2%)
Somnolence	0	3(1%)	0	1(2%)
Atelectasis	2(7%)	2 (<1%)	(1%)	0
Oliguria	0	4(2%)	2(2%)	0
Adverse Event	Placebo			
	Head and Neck (N=34)	Cardiac (N=206)	Laparotomy (N=87)	Other (N=52)
Patients with at least one treatment-emergent adverse event	17(50%)	143(69%)	44(51%)	34(65%)
Hypotension	1(3%)	36(17%)	5(6%)	6(12%)
Hypertension	7(21%)	32(16%)	18(21%)	11(21%)
Nausea	0	24(12%)	8(9%)	4(8%)
Bradycardia	0	10(5%)	0	0
Mouth dry	0	4(2%)	0	0
Fever	3(9%)	6(3%)	6(7%)	2(4%)
Vomiting	2(6%)	14(7%)	5(6%)	0
Atrial fibrillation	0	13(6%)	0	0
Hypoxia	0	10(5%)	0	4(8%)
Anemia	0	6(3%)	0	3(6%)
Pain	0	7(3%)	0	0
Tachycardia	3(9%)	7(3%)	4(5%)	4(8%)
Hemorrhage NOS	0	12(6%)	2(2%)	3(6%)
Pleural effusion	0	2 (<1%)	1 (1%)	1(2%)
Hypovolemia	0	9(4%)	1 (1%)	0
Thirst	0	1 (<1%)	0	0
Rigors	2(6%)	8(4%)	2(2%)	1(2%)
Hyperpyrexia	3(9%)	5(2%)	1 (1%)	1(2%)
Agitation	0	6(3%)	3(3%)	2(4%)
Somnolence	0	6(3%)	0	0
Atelectasis	0	9(4%)	2(2%)	2(4%)
Oliguria	1(3%)	2 (<1%)	0	0

Sponsor's Table 53 ISS Vol 8/10-239-154

a: Experienced by  $\geq 2\%$  of all dexmedetomidine-treated patients in Phase II/III continuous infusion ICU sedation studies

\*: Statistically significant difference between randomized dexmedetomidine patients and placebo patients.

Hypotension was significantly more common among all surgical groups receiving Dexmedetomidine as compared to placebo patients. Bradycardia was more common in the Head / Neck and Other surgical groups receiving Dexmedetomidine versus the placebo counterparts. The Dexmedetomidine patients in the Cardiac Surgery group had less rigors compared to the Cardiac Surgery patients receiving placebo.

## **SECTION 8.12 LONG TERM ADVERSE EFFECTS**

Sponsor reports that no obvious long term adverse effects have been associated with Dexmedetomidine administration. For the Phase II/III continuous infusion ICU sedation trials from the Abbott sponsored studies (exclusive of Japan), the total listing of all Serious Adverse Events reported for subjects/patient includes events from the time informed consent is signed to at least 30 days after participation in the Abbott sponsored trials. Long term administration studies of Dexmedetomidine have not been conducted.

## **SECTION 8.13 WITHDRAWAL EFFECTS**

Sponsor reports no withdrawal effects have been noted during the conduct of the Dexmedetomidine clinical programs.

## **SECTION 8.14 120 SAFETY UPDATE**

Sponsor states studies whose databases were not locked or that were ongoing at the time of the NDA submission and studies initiated after the submission are included in the 120 Day Safety Update. 3 Phase I and 4 Phase II studies are included; there are no Phase III studies in the presentation. Since the submission of the NDA, 159 subjects/patients have been enrolled in clinical studies conducted in the United States, Canada, and Europe. The sponsor appears to have provided safety information on 87 patients/subjects exposed to Dexmedetomidine in the 120 Day Safety Update presentation. Because of the limited number of new patients exposed to Dexmedetomidine since the NDA submission, the Sponsor did not integrate the new data with the data submitted in the NDA.

The Phase I studies had 3 premature discontinuations after exposure to Dexmedetomidine. The Phase II studies had no one discontinue prematurely but 2 deaths did occur. The deaths occurred in studies that remain blinded therefore treatment exposure is not clear. A request has been made to sponsor for Case Report Forms on the discontinuations.

The adverse events reported in the presentation are similar to that reported in the Integrated Summary of Safety: hypotension, hypertension, and bradycardia. Other adverse events reported were headache, nausea, and dry mouth. The occurrence of these

events appears similar to placebo treated individuals although tests of significance were not performed.

## SECTION 8.15 : SAFETY DISCUSSION

Sponsor claims the safety profile of Dexmedetomidine has been evaluated in more than 3300 patients in clinical studies conducted in the United States, Canada, Europe, and Japan. Safety data on 1770 patients has been submitted to the Agency in support of this NDA. Consequently, the safety profile for over 1500 patients/subjects is largely unknown. A request has been made to Abbott Laboratories to provide information on the following:

- A delineation of all the various doses of Dexmedetomidine administered.
- The time periods for which Dexmedetomidine was administered.
- Data on the incidence of deaths, discontinuations, and Serious Adverse Events between Dexmedetomidine, placebo, and active controls.
- The Case Report Forms for discontinuations presented in the 120 Day Safety Update.

The expected effects of an alpha-2 sympathetic agonist are central inhibition of sympathetic outflow at low to moderate doses and peripheral sympathomimetic activity at high doses. By understanding this pharmacology, the most frequently observed side effects of Dexmedetomidine are quite predictable:

- Hypertension during the high loading dose infusion as a result of peripheral sympathetic stimulation.
- Hypotension and bradycardia with the low maintenance dose infusion resulting from sympathetic inhibition and unopposed parasympathetic activity.

Because of technical reasons involving an experimental monitoring system that precluded the collection/analysis of some vital sign data, the only information summarized for vital signs is for the 576 continuous infusion ICU patients. In this subset of subjects, mean baseline systolic pressure was 126 mm Hg for both Dexmedetomidine patients and placebo patients. Systolic pressure rose about 7mmHg during the initial loading dosing and then decreased over the next 10 minutes. Hypotension occurred significantly more often in the Dexmedetomidine groups than the other comparator groups. Randomized Dexmedetomidine patients with an adverse event of hypotension showed a mean decrease in systolic pressure of 20-25mmHg during the first 20 minutes. The pattern of diastolic blood pressure in patients with hypotension is similar to the systolic changes.

Bradycardia occurred significantly more frequently with Dexmedetomidine. In the ICU subset, baseline rate was 81 beats per minute (bpm) in the placebo group vs 80 bpm in the Dexmedetomidine patients. Heart rates appeared to be about 10 bpm slower during Dexmedetomidine infusion than in the placebo groups.

Changes from baseline in clinical laboratory parameters were presented for patients from the continuous infusion studies. Data on approximately 1000 patients was summarized. Of note, Dexmedetomidine patients had statistically significantly lower hematocrit and hemoglobin values than placebo groups. Dexmedetomidine patients had significantly higher blood glucose values than the placebo groups. Pharmacology reviewer Dr. Geyer noted Dexmedetomidine treated animals showed a 300% increase in blood glucose levels along with glucosuria. However, in the human trials neither the hematology nor the glucose differences were of clinical significance.

The incidence of deaths/premature discontinuations/serious adverse events for Dexmedetomidine versus placebo or versus active controls is not clear. Sponsor has been asked to provide such information. The review of deaths and premature discontinuations and ascribing a possible association with Dexmedetomidine is difficult because of multiple confounding variables. Most of the patients were elderly with multiple pre-existing medical problems undergoing extensive surgical procedures. None of the deaths appear related to Dexmedetomidine. 12 patients were discontinued prematurely because of hypotension, bradycardia, or oversedation. These 12 prematurely discontinued individuals appear to have a likely association with Dexmedetomidine administration.

One subject was discontinued prematurely because of asthma symptoms. It is not clear if Dexmedetomidine was causal for the asthma in this individual. Inhibition of sympathetic activity is known to initiate or exacerbate bronchospasm particularly in susceptible individuals. Consequently, Dexmedetomidine probably should be used with caution in patients with bronchospastic disease.

Pharmacologist Dr Geyer noted keratitis and lens opacities in preclinical studies. While only one report of conjunctivitis secondary to a corneal abrasion was seen in the clinical Phase II/III studies, xerophthalmia was reported on several occasions in Phase I trials in patients receiving Dexmedetomidine. Sponsor claims the eye findings in the animals were due to decreased lacrimal secretions and decreased blinking. Decreased eye lubrication may suggest the need for eye protection during human use.

Drug interaction studies were carried out with Dexmedetomidine and alfentanil/isoflurane/midazolam/rocuronium/propofol. Tests of significance for comparisons were not performed. The most notable safety concerns involved the Dexmedetomidine-midazolam combination. Somnolence occurred in 100% of this group versus 11% of the comparative placebo-midazolam comparator group. Hypotension was more common with Dexmedetomidine-midazolam (95%) than placebo-midazolam (11%). Sponsor suggests midazolam doses should be reduced when administered with Dexmedetomidine.

Pharmacologist Dr Geyer noted some preclinical data that showed animals exposed to Dexmedetomidine exhibited decreased left ventricular output as compared to controls. In human trials few patients had Cardiac Output data measured; among those that did, sponsor states that no differences were noted between the groups. Central Venous Pressure (CVP) measurements revealed Dexmedetomidine exposed patients had smaller

(about 0.5 mm Hg) but statistically significantly lower values than placebo groups. This would be in keeping with Dexmedetomidine actions to inhibit sympathetic outflow.

In summary, for the subjects and information presented for review, Dexmedetomidine appears to be a reasonably safe agent. However, the database for vital signs is based only on the 576 continuous infusion ICU patients; this appears to be a small sample. As would be expected, bradycardia and hypotension are the side effects that would predictably occur and indeed they were the most common side effects with the low maintenance doses while elevation of blood pressure occurred with higher loading doses. The other noted findings of Dexmedetomidine, xerophthalmia, hyperglycemia, potentiation of midazolam, possible lower CVP and cardiac outputs, and possible potentiation of bronchospastic disease should be noted in labeling.

### SECTION 9.0 DISCUSSION

Based on the information available at this time, Dexmedetomidine is an effective agent for independently providing sedation in an Intensive Care setting. While Dexmedetomidine is capable of potentiating analgesic agents, the sponsor did not demonstrate that Dexmedetomidine can independently provide analgesia in an ICU setting. With appropriate precautions, Dexmedetomidine is a safe agent for its intended use.

### SECTION 10.0 RECOMMENDATIONS

Presuming review of additional material is acceptable, recommend approval of the application.

*see also Addenda #1 + #2 by Dr. Hartwell  
 find - new memo dated November 5, 1999*  
*ISI*  
*ISI*  
*November 5, 1999*

Charles R. Cortinovia, MD MPH  
 24 August, 1999

**APPENDIX 1****RAMSAY SEDATION SCORE:**

The level of sedation was assessed using a 6 point nominal scale modified from Ramsay

6 = asleep, no response

5 = asleep, sluggish response to light glabellar tap or loud auditory stimulus

4 = asleep but with brisk response to light glabellar tap or loud auditory stimulus

3 = patient responds to commands

2 = patient cooperative, oriented, and tranquil

1 = patient anxious, agitated, or restless

**APPEARS THIS WAY  
ON ORIGINAL**

NDA: #21-038

SEP 13 1999

NAME: Dexmedetomidine HCL for Infusion

SPONSOR: Abbott Laboratories

REVIEW DATE: 09-13-99

TYPE OF REVIEW: Addendum to NDA

REVIEWER: Patricia Hartwell, MD MBA

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**ADDENDUM TO MEDICAL OFFICER REVIEW**

**PART I - ADDITIONAL 120-DAY SAFETY UPDATE INFORMATION**

The sponsor has provided additional information on deaths, discontinuations, and serious adverse events in the Phase I and Phase II studies that were cited in the 120-day safety update of the original NDA review. This information is summarized below.

**DEATHS:**

Phase I

There have been no deaths reported in the three studies included in this update.

Phase II

*Study W98-263 (Subject 104)*

- A 79-year-old female patient with cardiac failure, chronic renal failure, and respiratory insufficiency was admitted to the ICU following a myocardial infarction and cardiac arrest. She was entered into an ongoing double-blind continuous infusion study. She suffered 6 serious adverse events including two episodes of hypotension and bradycardia (4 events) that were possibly related to administration of the study drug. The infusion was continued for a total of 18 hours until the decision was made to withdraw all supportive care. At this time the infusion of dexmedetomidine and all other medications were discontinued and the patient succumbed to her multi-organ failure shortly thereafter. Although it appears from the available information that the patient's ultimate demise was a result of her multi-organ failure, this reviewer

disagrees with the sponsor that the administration of dexmedetomidine is not related to the death. From the information provided in the Case Report Form, the patient's condition was such that death was the most likely outcome for this ICU hospitalization. However, Dexmedetomidine was infusing during the time of the patient's worsening condition and, therefore, it is not possible to rule this agent in or out as a contributing or hastening factor in the patient's ultimate demise.

*Study W98-264 (Subject 101)*

- A 58-year-old male ICU patient with liver failure, renal failure, aspiration pneumonia, and septicemia was entered into a sedation continuous infusion study. Although the patient did suffer two episodes of hypotension that may have been related to the dexmedetomidine infusion, these episodes were transient in nature and responded readily to decreasing the infusion rate. The infusion was continued for a total of fifty hours until the patient's relatives made the decision to withdraw all supportive care. At this time the infusion of dexmedetomidine and all other medications were discontinued and the patient succumbed to his multi-organ failure shortly thereafter. Although it appears from the available information that the patient's ultimate demise was a result of his multi-organ failure, this reviewer disagrees with the sponsor that the administration of dexmedetomidine is not related to the death. From the information provided in the Case Report Form, the patient's condition was such that death was the most likely outcome for this ICU hospitalization. However, Dexmedetomidine was infusing during the time of the patient's worsening condition and, therefore, it is not possible to rule this agent in or out as a contributing or hastening factor in the patient's ultimate demise.

**DISCONTINUATIONS:**

Phase I

There were three patients in Phase I studies who were discontinued after receiving the study drug:

*Study W98-272 (Subject 010)*

- 27 yr old male who received 0.6 mcg/kg/hr dose of study drug and failed to return for 2<sup>nd</sup> and 3<sup>rd</sup> visits to complete the protocol administration. No adverse events were recorded during first visit.

*Study W98-273 (Subject 109)*

- Subject received an uncertain amount of a 0.3 ng/ml dose when it was discovered that the urinalysis collected prior to administration of the study drug was abnormal. The subject was discontinued and advised to followup with his PMD.

*Study W98-273 (Subject 226)*

- Subject suffered a seizure after receiving a 1.25 ng/ml infusion of the study drug and was prematurely discontinued (see Serious Adverse Events below).

Phase II

There have been no premature discontinuations in the Phase II studies although three of the studies are currently ongoing.

**SERIOUS ADVERSE EVENTS:**Phase I*Study W98-273 (Subject 226)*

- Subject had received an infusion of 1.25 ng/ml of the study drug for approximately 18.5 hours (24 hours dictated by protocol) when he suffered a single seizure of approximately 1.5-2 minutes in duration. Subject subsequently complained of short term memory loss, dizziness, and myalgias consistent with the post-ictal state. Although the subject had no history of a seizure disorder, he had suffered an episode of head trauma two years prior to this occurrence. However, even in light of this history, it is not possible to completely exclude the study drug as a causative agent.

Phase II*Study DEX-96-017 (Subject 101)*

- Subject in the 0.3 ng/ml dexmedetomidine arm of a double blind study in CABG patients received an overdose due to a computer malfunction. This overdose was apparently discovered 11 hours into a 12-hour infusion. During the time of infusion the patient had one short episode of hypotension requiring treatment with an alpha-blocking agent and one episode of bradycardia requiring treatment with an anticholinergic and activation of an existing pacemaker. While the patient's underlying cardiac disease and residual effects from the CABG procedure may be responsible for the noted hemodynamic instability, it is not possible to completely exclude the study drug as a causative agent.

*Study DEX-96-017 (Subject 103)*

- Subject in the placebo arm of a double blind study in CABG patients experienced a serious post-operative hemorrhage that was considered to be related to the surgical procedure.

*Study W98-263 (Subject 103)*

- Subject in a double-blind study of ICU patients developed a wound infection in an abdominal laparotomy incision. This adverse event was considered to be related to the patient's underlying surgical pathology and not to administration of the study agent.

*Study W98-263 (Subject 104)*

- Discussed in section on "Deaths" above

*Study W98-264 (Subject 101)*

- Discussed in section on "Deaths" above

*Study W98-264 (Subject 102)*

- Subject in an open-label study of ICU patients suffered four serious adverse events: ileus, hypoxia, respiratory insufficiency, and hypercapnia. Infusion of the study drug had been completed five days prior to the occurrence of these events and they were therefore considered related to the patient's underlying chronic respiratory insufficiency. The patient was reintubated, sedated, ventilated, and given medication for the ileus.

*Study W98-274 (Subject 002)*

- Subject in double-blind ICU study suffered respiratory insufficiency and failure necessitating re-intubation and mechanical ventilation. This adverse event was considered to be secondary to an existing pneumonia and unrelated to the study agent.

*Study W98-274 (Subject 007)*

- Subject in double-blind ICU study suffered a post-operative hemorrhage requiring surgical intervention. This adverse event was considered to be a post-surgical complication and unrelated to the study agent.

*Study W98-274 (Subject 029)*

- Subject in double-blind ICU study suffered a post-operative hemorrhage requiring surgical intervention. This adverse event was considered to be a post-surgical complication and unrelated to the study agent.

The overall incidence of adverse events, serious adverse events, and deaths in the 120-day safety update were consistent with that reported in the original and supplementary NDA submissions.

**Part II - INTEGRATED SUMMARY OF SAFETY SUPPLEMENT (Aug 16, 1999)**

**OVERVIEW:**

The sponsor referenced 57 Abbott-sponsored studies and 2 Abbott-sponsored studies conducted in Japan in their original NDA submission. However, this data was not included in their final ISS database. They were asked to provide the following information to the agency and to integrate this information as appropriate into a Supplemental ISS database:

- Integrated extent of exposure data

- Integrated safety data, specifically adverse events, serious adverse events, deaths, and discontinuations
- Study-specific explanation of data integrity and availability, or lack thereof
- Study-specific delineation of safety data
- CRF, CRT, or any other available information on death in study 3005006, patient #211
- CRF, CRT, or any other available information on Phase I and Phase II study Japanese patients with adverse events

#### DATA ISSUES:

In response to a request for an explanation of the exclusion of the study data from the NDA Integrated Summary of Safety, the sponsor has submitted the following information.

According to the sponsor, the [redacted] were initiated as early as 1988 and were pilot or exploratory studies, looking at potential doses, administration modes, and indications. Since 1997 Dexmedetomidine has been investigated primarily as a treatment in the ICU for sedation with analgesic properties. None of the [redacted] addressed this indication. The initial NDA submission contained 56 separate synopses of the [redacted] data, incorporating 57 studies, and a tabulation of the available safety data was included. It was stated that 14 out of the 57 studies were conducted under GCP as [redacted], and that Case Report Forms were available for 52 of the 57 studies.

The sponsor has made an attempt to confirm GCP compliance on the 14 studies as defined [redacted] but has been unable to do so. The re-evaluation has found deficiencies including absences of study drug accountability, protocol amendments, and CRF approval. In addition, audits of one study found that the data entry error rate was 10 times higher than the sponsor's standard. Although it was initially stated that Case Report Forms were available for 52 of the 57 studies, in fact the only information available for 10 of those studies was on data collection sheets that did not capture protocol-specified parameters for adverse events. Specifically missing were date of onset, duration of the event, relationship to study drug, outcome, action taken, and intensity of event.

The tables below incorporate this new information and summarize the number of studies and subjects included in the supplemental database that had available CRFs and that were conducted under GCP's as originally [redacted]

Table 1: [redacted] Studies Included in Supplemental ISS

	Phase I	Phase II	Phase III
<i>N</i> Total	19	27	11
# in Supplemental ISS	9 (47.4%)	23 (85.2%)	11 (100%)
# with CRF's	8 (42.1%)	23 (85.2%)	11 (100%)
# with GCP's	3 (15.8%)	2 (7.4%)	9 (81.8%)

Table 2: Subjects Included in Supplemental ISS

	Phase I	Phase II	Phase III
<i>N Total</i>	171	766	586
<i># in Supplement ISS</i>	95 (55.6%)	729 (95.2%)	586 (100%)
<i># with CRF's</i>	67 (39.2%)	729 (95.2%)	586 (100%)
<i># with GCP's</i>	26 (15.2%)	46 (6%)	522 (89.1%)

## EXTENT OF EXPOSURE:

Data from Abbott-sponsored studies conducted in the US, Europe, and Japan and for non-Abbott-sponsored studies conducted \_\_\_\_\_ was compiled as possible and submitted in the safety supplement. An analysis of the total number of exposed patients contained in the original NDA review (Medical Officer Review, Table 32, p. 57) has been updated to incorporate the newly submitted information and is presented in the following table.

Table 3: Exposed Patients (Updated)  
Abbott, \_\_\_\_\_ Japanese Data

	Phase I Studies					Phase II/III Studies		
	Continuous Infusion	Rapid Infusion	Intra-Muscular	Trans Dermal	Oral	Continuous Infusion	Rapid Infusion	Intra-Muscular
Number of Studies (Includes Crossovers)	13	19	5	2	1	23	12	14
Number of Crossover Studies	7	5	3	1	1	0	0	0
Dex Exposed Subjects	184	245	54	25	12	1703	423	692
Placebo Exposed Subjects	101	44	26	N/A	N/A	984	165	314
Comparator Exposed Subjects	12	5	12	N/A	N/A	0	96	286

Exposure	Total Subjects
Dexmedetomidine	3083
Placebo	1600
Comparator	411

Based on Sponsor's Tables A & E; Supplemental ISS; Tables 1.1.1, 1.2.1, 1.3.1, 1.4.1, 1.5.1, 2.1.1, 2.2.1.1, 2.3.1, Supplemental ISS  
Subjects may be counted in more than one study if crossover study

According to the sponsor, some of the data for \_\_\_\_\_ d and Abbott-sponsored Japanese studies was not included in the supplemental safety database because of the unavailability of Case Report Forms or the omission of safety data from Case Report Forms that do exist (Sponsor Tables A, E; pg. 3,8; Supplemental ISS). Eleven Phase I studies with 109 subjects and four Phase II/II studies with 146 subjects have been categorized by the sponsor as containing inadequate information and this data has not

been submitted to the NDA safety supplement. Therefore, the remainder of the analysis of the Integrated Summary of Safety supplement has been conducted on a dexmedetomidine exposure group of 3083 subjects.

Extent of exposure for some of the \_\_\_\_\_ studies was not available, either because the information was not included in the CRF or because the CRF was unobtainable. Where data was not available, extent of exposure was extrapolated from protocol-derived intended exposure. Extent of exposure, as submitted in the original ISS and as updated in the ISS supplement, is presented in the following tables.

**Table 4: Phase I Studies Extent of Exposure  
Continuous Infusion, Rapid Infusion, Intramuscular Injection**

	Continuous Infusion  ISS	Continuous Infusion ISS Supplement	Rapid Infusion  ISS	Rapid Infusion ISS Supplement	IM Administration ISS Supplement
Mean Total Dose N (mcg/kg) ± SD	168 3.53 ± 4.04	174 3.52 ± 3.97	117 0.56 ± 0.24	184 0.90 ± 0.63	36 3.86 ± 3.33
Mean Total Duration N (hr) ± SD Minimum Maximum	168 7.71 ± 8.40 0.72 24.02	174 7.65 ± 8.26 0.72 24.02	117 0.17 ± 0.00 0.17 0.18	167 0.13 ± 0.05 0.02 0.18	10 0.02 ± 0.00 0.02 0.02

Based on Sponsor's Table B, ISS Supplement, Aug 16, 99, p.4

**Table 5: Phase II/III Studies Extent of Exposure  
Continuous Infusion, Rapid Infusion, Intramuscular Injection**

	Continuous Infusion  ISS	Continuous Infusion ISS Supplement	Rapid Infusion ISS Supplement	IM Administration ISS Supplement
Mean Total Dose N (mcg/kg) ± SD	1334 4.57 ± 3.18	1518 4.29 ± 3.09	267 1.00 ± 0.67	662 1.91 ± 0.75
Mean Total Duration N (hr) ± SD Minimum Maximum	1336 10.89 ± 6.35 0.12 39.58	1475 10.10 ± 6.54 0.02 39.58	106 0.05 ± 0.03 0.02 0.17	N/A

Based on Sponsor's Table E, ISS Supplement, Aug 16, 99, p.9

#### DEATHS, DISCONTINUATIONS, ADVERSE EVENTS:

The sponsor has provided information in the Integrated Summary of Safety Supplement on the numbers of deaths, discontinuations, and adverse events for each referenced treatment group (dexmedetomidine, placebo, comparator) contained in their updated safety database. This information has been compiled in the following tables.

**Table 6: Phase I Studies  
Discontinuations, Deaths, Adverse Events by Treatment Group**

N (%)	Dexmedetomidine		Placebo		Comparator	
	Abbott	All	Abbott	All	Abbott	All
Treated	285	431	97	111	12	17
Discontinued	6 (2%)	7 (2%)	0	0	0	0
Unknown	0	0	0	0	0	0
At Least 1 AE	176 (62%)	236 (55%)	55 (57%)	56 (50%)	0	3 (18%)
At Least 1 Treatment Emergent AE	175 (61%)	222 (52%)	48 (49%)	49 (44%)	0	0
Deaths	0	0	0	0		

Based on Sponsor's Tables 1.1.1 - 1.5.3.2, p. 24-59, ISS/

**Table 7: Phase II/III Studies  
Discontinuations, Deaths, Adverse Events by Treatment Group**

N (%)	Dexmedetomidine		Placebo		Comparator	
	Abbott	All	Abbott	All	Abbott	All
Treated	1337	2652	817	1384	0	390
Discontinued	55 (4%)	107 (4%)	34 (4%)	74 (5%)	0	0
Unknown	1 (<1%)	801 (30%)	1 (<1%)	257 (19%)	0	356 (91%)
At Least 1 AE	886 (66%)	1670 (63%)	515 (63%)	771 (56%)	0	258 (66%)
At Least 1 Treatment Emergent AE	814 (61%)	1519 (57%)	477 (58%)	708 (51%)	0	219 (56%)
Deaths	12 (0.9%)	13 (0.5%)	8 (<1%)	8 (<1%)		

Based on Sponsor's Tables 2.1.1 - 2.5.3.2, p. 62-114, ISS/

**Table 8: All Studies  
Discontinuations, Deaths, Adverse Events by Treatment Group**

N (%)	Dexmedetomidine		Placebo		Comparator	
	Abbott	All	Abbott	All	Abbott	All
Treated	1622	3083	914	1495	12	407
Discontinued	61 (4%)	114 (4%)	34 (4%)	74 (5%)	0	0
Unknown	1 (<1%)	801 (26%)	1 (<1%)	257 (17%)	0	356 (87%)
At Least 1 AE	1062 (65%)	1906 (62%)	570 (62%)	827 (55%)	0	261 (64%)
At Least 1 Treatment Emergent AE	989 (61%)	1741 (56%)	525 (57%)	757 (51%)	0	219 (54%)
Deaths	12 (0.7%)	13 (0.4%)	8 (<1%)	8 (<1%)		

Based on Sponsor's Tables 1.1.1 - 2.

24-114, ISS/

**DEATHS:**

Additional information has been provided on the single death in the studies.

*Study 3005006 (Subject 211)*

The subject was a 73-year-old male with a medical history that included the presence of Type II Diabetes Mellitus, remote use of cigarettes, history of a myocardial infarction with now stable angina, and severe three-vessel disease on cardiac catheterization. He was a participant in a study where he received an undefined dose of dexmedetomidine during elective coronary artery bypass grafting surgery and a continuous infusion for an undefined period post-operatively. The patient's post-operative course was complicated by hyperglycemia, acidosis, hemodynamic instability, and decreased urine output. He was extubated within the first 24 hours but sometime thereafter became agitated and confused, requiring sedation and supplemental oxygen to maintain his saturation. Three days after surgery the patient's intravenous line became disconnected, there was massive blood loss, and the patient died. The investigators conclude that the patient's death was not attributable to the study drug.

On the basis of the information provided, this reviewer has made the following conclusions about the event. The patient's post-operative course, although complicated, was not unusual or unexpected following coronary artery bypass grafting on an individual with such a medical history. The onset of agitation and confusion was most likely multifactorial, a combination of cerebral hypoperfusion, hypoxia, and metabolic derangement. However, dexmedetomidine may also have contributed to the onset of confusion and cannot be eliminated as a factor.

No detailed information has been given about the events surrounding the patient's death other than a notation of massive blood loss from a disconnected intravenous line. This incident occurred three days after the dexmedetomidine infusion had been discontinued. However, if dexmedetomidine was a contributor or initiator of the patient's confusional state and if the patient's ongoing confusion and agitation was the cause of an inadvertent intravenous disconnection, the study agent must be secondarily implicated in this patient's death. From the data provided, it is not possible to completely discount dexmedetomidine as a factor in the initial agitation/confusion episode.

**DISCONTINUATIONS:**

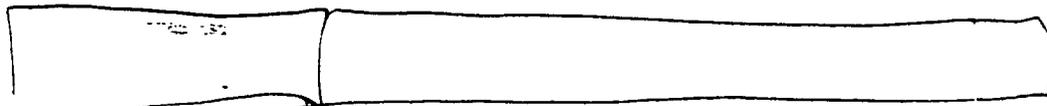
No additional information was requested nor was provided about the discontinuations in the Abbott-sponsored Japanese studies.

**SERIOUS ADVERSE EVENTS:**

Serious adverse events for \_\_\_\_\_ studies have been discussed in detail in the original NDA Medical Officer Review. No additional information was requested nor was any provided by the sponsor in their additional submission.

The sponsor was requested to provide additional information on Subject #9 from the Abbott-sponsored Japanese Phase I study J-DEX-9501. This subject had not been reported in the serious adverse event database by the investigator. According to the supplemental information, this subject was a healthy Japanese male undergoing a voluntary infusion study. Two hours and 50 minutes after completion of a dexmedetomidine infusion (0.6 mcg/kg intravenously over 10 minutes), the patient experienced nausea, hypotension, atrioventricular junctional rhythm, and bradycardia, all of which were reversed by the administration of 0.5 mg atropine sulfate. Two episodes of single ventricular extrasystole were observed on the ECG tracing over 6 hours after completion of the dexmedetomidine infusion. These episodes resolved spontaneously and did not recur. No other adverse events were noted for this subject and all reactions above resolved without sequelae.

From the information provided, this reviewer concludes that dexmedetomidine may have been a contributing factor to the first series of adverse events in this subject. Bradycardia, hypotension, and vagotonic effects are in keeping with this agent's side effects profile and, despite the fact that the infusion had been completed almost three hours prior to occurrence of the events, it is possible for some residual effects to occur within this time span. It is unlikely that the second set of events, ventricular extrasystole, were related to the administration of dexmedetomidine, due to the significant temporal separation between the end of the infusion and the occurrence of the events.

**ALL ADVERSE EVENTS:****PHASE I STUDIES**

In the Phase I studies, 56% of all Dexmedetomidine treated subjects and 57% of all placebo treated subjects experienced at least one adverse event. The additional information submitted by the sponsor did not alter the fact that the most frequently experienced adverse events among dexmedetomidine treated subjects were dry mouth

(19%), somnolence (16%), headache (15%), and hypotension (12%). The most frequent adverse events among placebo treated patients were headache (16%), nausea (9%), and hyperkinesia (8%). It should be noted that, with the exception of fatigue, no adverse event was reported with more frequency in the dexmedetomidine-treated than in the Abbott dataset. The following table compares the frequency of adverse events in the dexmedetomidine and placebo treated subjects from the original ISS database and in the supplemental information provided by the sponsor.

Table 9 Treatment Emergent Adverse Events Experienced by ≥2% of Phase I Subjects

Adverse Event	Dexmedetomidine ISS (Abbott) N = 285	% Difference	Dexmedetomidine ISS Supplement N = 372	Placebo N = 97
At least one Treatment Emergent Adverse Event	175 (61%)	(-21%)	210 (56%)	48 (49%)
Mouth dry	59 (21%)	(-8%)	70 (19%)	6 (6%)
Somnolence	35 (12%)	(-13%)	60 (16%)	4 (4%)
Headache	49 (17%)	(-9%)	56 (15%)	15 (15%)
Hypotension	51 (18%)	(-16%)	45 (12%)	14 (14%)
Nausea	18 (6%)	(-5%)	19 (5%)	9 (9%)
Hypertension	18 (6%)	(-6%)	18 (5%)	3 (3%)
Dizziness	16 (6%)	(-6%)	16 (4%)	3 (3%)
Bradycardia	17 (6%)	(-4%)	12 (3%)	0 (0%)
Muscle contractions involuntary	13 (5%)	(0%)	17 (5%)	0 (0%)
Pallor	9 (3%)	(-3%)	9 (2%)	6 (6%)
Apnea	10 (4%)	(-4%)	10 (3%)	2 (2%)
Stupor	9 (3%)	(-3%)	9 (2%)	1 (1%)
Hyperkinesia	7 (2%)	(-2%)	7 (2%)	8 (8%)
Pain	8 (3%)	(-3%)	8 (2%)	1 (1%)
Pharyngitis	8 (3%)	(-3%)	8 (2%)	2 (2%)
Paresthesia	8 (3%)	(-2%)	9 (2%)	0
Xerophthalmia	8 (3%)	(-3%)	8 (2%)	1 (1%)
Fatigue	7 (2%)	(12%)	19 (5%)	11 (11%)
Hallucination	7 (2%)	(-2%)	7 (2%)	0
Vomiting	5 (2%)	(-2%)	5 (1%)	4 (4%)
Agitation	6 (2%)	(-2%)	6 (2%)	4 (4%)
Pruritus	6 (2%)	(-2%)	6 (2%)	4 (4%)
Rhinitis	5 (2%)	(-2%)	5 (1%)	1 (1%)
Back pain	5 (2%)	(-2%)	5 (1%)	1 (1%)
Vision abnormal	5 (2%)	(-2%)	5 (1%)	3 (3%)
Abdominal pain	5 (2%)	(-2%)	5 (1%)	1 (1%)
Conjunctivitis	5 (2%)	(-2%)	5 (1%)	0

Shading added by reviewer to highlight clinically significant differences. Modified Sponsor's Table 16 ISS Vol 8/10-239-52, Tables C & D 15

pg 6-7, Table, Sponsor Response, Sept 1, 1999, p. 7.

PHASE II/III STUDIES

In the Phase II/III continuous infusion studies, 57% of all Dexmedetomidine treated subjects and 57% of all placebo treated subjects experienced at least one adverse event. The additional information submitted by the sponsor did not alter the finding that the most frequently experienced adverse events among dexmedetomidine treated subjects were hypotension (24%), hypertension (11%), nausea (12%), and bradycardia (7%). The most frequent adverse events among placebo treated patients were hypotension (15%), hypertension (15%), and nausea (13%). It should be noted that, with the exception of nausea, vomiting, pain, and dry mouth, no other adverse events were reported with more frequency in the dexmedetomidine-treated than the Abbott dataset. The following table compares the frequency of adverse events in the dexmedetomidine and

placebo treated subjects from the original ISS database and in the supplemental information provided by the sponsor.

**Table 10 Treatment Emergent Adverse Events Experienced by ≥2% of Phase II/III Subjects Continuous Infusion Studies**

Adverse Event	Dexmedetomidine ISS (Abbott) N = 1337	% Difference	Dexmedetomidine ISS Supplement N = 1703	Placebo ISS N = 817	Placebo ISS Supplement N = 984
At least one Treatment Emergent Adverse Event	814 (61%)	(-17%)	976 (57%)	477 (58%)	559 (57%)
Hypotension	392 (29%)	(-26%)	402 (24%)	131 (16%)	143 (15%)
Hypertension	178 (13%)	(-11%)	185 (11%)	135 (17%)	143 (15%)
Nausea	162 (12%)	(-1%)	210 (12%)	105 (13%)	126 (13%)
Bradycardia	95 (7%)	(0%)	119 (7%)	25 (3%)	32 (3%)
Tachycardia	65 (5%)	(-3%)	73 (4%)	62 (8%)	69 (7%)
Fever	61 (5%)	(-4%)	66 (4%)	42 (5%)	45 (5%)
Hypoxia	58 (4%)	(-4%)	59 (3%)	36 (4%)	37 (4%)
Anemia	52 (4%)	(-3%)	56 (3%)	24 (3%)	27 (3%)
Vomiting	48 (4%)	(3%)	74 (4%)	43 (5%)	62 (6%)
Hemorrhage NOS	36 (3%)	(-1%)	45 (3%)	22 (3%)	27 (3%)
Pain	34 (3%)	(5%)	64 (4%)	19 (2%)	32 (3%)
Rigors	33 (2%)	(-1%)	35 (2%)	27 (3%)	27 (3%)
Atrial fibrillation	33 (2%)	(0%)	40 (2%)	19 (2%)	23 (2%)
Mouth dry	30 (2%)	(3%)	50 (3%)	4 (<1%)	8 (<1%)
Agitation	30 (2%)	(0%)	36 (2%)	27 (3%)	28 (3%)

Shading added by reviewer to highlight clinically significant difference in frequency from placebo  
 Modified Sponsor's Table 18 ISS Vol 1/10-239-52, Table G ISS Supplement, Aug 16 1999, pg 11, Table, Sponsor Response, Sept 1, 1999, p. 7.

In the Phase II/III rapid infusion studies, 61% of all Dexmedetomidine treated subjects and 46% of all placebo treated subjects experienced at least one adverse event. The most frequently experienced adverse events among dexmedetomidine treated subjects were pain (34%), vomiting (31%), dry mouth (13%), and bradycardia (8%). The most frequent adverse events among placebo treated patients were also pain (23%), vomiting (20%), and dry mouth (23%), although bradycardia (2%) was relatively infrequent. The table below compares the frequency of adverse events in the dexmedetomidine and placebo treated subjects in the combined supplemental database.

**Table 11 Treatment Emergent Adverse Events Experienced by ≥2% of Phase II/III Subjects Rapid Infusion Studies**

Adverse Event	Dexmedetomidine ISS Supplement N = 267	Placebo ISS Supplement N = 105
At least one Treatment Emergent Adverse Event	162 (61%)	48 (46%)
Pain	90 (34%)	24 (23%)
Vomiting	83 (31%)	21 (20%)
Mouth Dry	34 (13%)	24 (23%)
Bradycardia	22 (8%)	2 (2%)
Headache	18 (7%)	10 (10%)
Paresthesia	11 (4%)	4 (4%)
Nausea	11 (4%)	2 (2%)
Urinary Retention	8 (3%)	5 (5%)
Hypotension	8 (3%)	1 (<1%)
Agitation	6 (2%)	0
Fatigue	5 (2%)	0
Somnolence	4 (1%)	3 (3%)

Shading added by reviewer to highlight clinically significant difference in frequency from placebo  
 Modified Sponsor's Table H ISS Supplement, Aug 16 1999, pg 12.

In the Phase II/III intramuscular studies, 56% of all Dexmedetomidine treated subjects and 34% of all placebo treated subjects experienced at least one adverse event. The most frequently experienced adverse events among dexmedetomidine treated subjects were pain (32%), vomiting (19%), dry mouth (16%), and somnolence (13%). The most frequent adverse events among placebo treated patients were also pain (18%), vomiting (9%), and dry mouth (8%), although somnolence (4%) was relatively infrequent. It should also be noted that while the frequency of bradycardia in the dexmedetomidine group was 10%, the placebo group reported a less than 1% frequency of this adverse event. The table below compares the frequency of adverse events in the dexmedetomidine and placebo treated subjects in the combined supplemental database.

**Table 12 Treatment Emergent Adverse Events Experienced by  $\geq 2\%$  of Phase II/III Subjects Intramuscular Studies**

Adverse Event	Dexmedetomidine ISS Supplement N = 682	Placebo ISS Supplement N = 295
At least one Treatment Emergent Adverse Event	381 (56%)	101 (34%)
Pain	216 (32%)	53 (18%)
Vomiting	132 (19%)	28 (9%)
Mouth Dry	106 (16%)	23 (8%)
Somnolence	92 (13%)	13 (4%)
Dizziness	77 (11%)	22 (7%)
Bradycardia	71 (10%)	2 (<1%)
Nausea	52 (8%)	25 (8%)
Hyperkinesia	37 (5%)	12 (4%)
Urinary Retention	24 (4%)	8 (3%)
Hypotension	18 (3%)	2 (<1%)
Fatigue	12 (2%)	0

Shading added by reviewer to highlight clinically significant difference in frequency from placebo  
Modified Sponsor's Table I ISS Supplement, Aug 13 1999, pg. 13.

No information to supplement the original NDA submission on laboratory findings, drug-drug interactions, drug-demographic interactions, or long term adverse effects was provided by the data from the \_\_\_\_\_ ps.

### ABBOTT-SPONSORED JAPANESE STUDIES

The sponsor was asked to provide any available information on three subjects in the Japanese Phase I study J-DEX-9501. These subjects had been previously identified as experiencing hematological changes during the course of the study. The study involved 9 healthy volunteer Japanese males who underwent three separate infusions of dexmedetomidine (0.1, 0.3, and 0.6 mcg/kg). The sponsor provided laboratory data on 7 of the 9 subjects that included baseline, 24-hour post-treatment, and 72-hour post-treatment values. In some cases, 2-week post-treatment values were provided. Analysis of the available information reveals that, while 6 of the 7 patients experienced decreases

in hemoglobin and hematocrit during the course of the study, these decreases were not clinically significant and were consistent with that reported in the original NDA submission.

**SUMMARY:**

By the sponsor's admission, one of the major difficulties in assessment sponsored and Abbott-sponsored Japanese data was the under-reporting of adverse events. Instructions to the investigators performing these studies regarding adverse event reporting and categorization were not explicit and apparently contributed to this problem. Consequently, the reported incidences of many treatment-emergent adverse events were below those in the original ISS submission.

In summary, after review of all supplemental information on \_\_\_\_\_ and Japanese studies provided by the sponsor (see listing below), the newly defined safety profile of dexmedetomidine is consistent with that reported in the Medical Officer's Review of the original NDA submission and this agent is considered reasonably safe for its intended use.

Information accessed and analyzed for this review:

- Amendment to NDA (8-17-99) – overview ISS supplement, AE summaries of Japanese studies, statistical summary tables
- Amendment to NDA (9-2-99 - CRF's for deaths as requested, laboratory value summaries for Japanese study
- Amendment to NDA (9-3-99) – explanation of data integrity, summary tables of treatment emergent adverse events, study-specific tables of adverse events
- Amendment to NDA (9-10-99) – CRF for subject in Japanese study as requested

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 ISI  
 PD  
 Patricia Hartwell, MD MBA  
 Medical Officer

CC: Division File  
 Original NDA #20-984  
 HFD-170 Patricia Hartwell, MD MBA  
 HFD-170 R.A. Rappaport, MD  
 HFD-170 Project Manager: Susmita Samanta

NDA: #21-038

NAME: Dexmedetomidine HCL for Infusion

SPONSOR: Abbott Laboratories

REVIEW DATE: 10-27-99

TYPE OF REVIEW: Addendum to NDA

REVIEWER: Patricia Hartwell, MD MBA

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**SECOND ADDENDUM TO MEDICAL OFFICER REVIEW OF NDA**

***PART I - EXTENT OF EXPOSURE***

The sponsor was asked to provide additional data on extent of exposure for all treated patients in the dexmedetomidine clinical studies. The information provided on the Phase I and the Phase II/III continuous infusion studies is summarized in the tables below.

Table 1      **Extent of Exposure - Frequency of Duration by Dose  
Phase I Continuous Infusion Studies - All-Treated Patients**

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

From Sponsor's Table of Duration by Dose, Supplement to NDA, 10-27-99, Exhibit I

**Table 2**                      **Extent of Exposure – Frequency of Duration by Dose**  
**Phase II/III Continuous Infusion Studies – All-Treated Patients**

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

From Sponsor's Table of Duration by Dose, Supplement to NDA, 10-27-99, Exhibit 4

## ***PART II – SERIOUS ADVERSE EVENT ANALYSIS***

### Phase I

There were 285 subjects in Abbott-sponsored studies and 146 subjects in non-Abbott-sponsored studies exposed to dexmedetomidine during Phase I trials (ISS Supplement, Tables 1.1.1-1.5.3.2, p. 24-59.). Two of the Abbott subjects experienced serious adverse events during the course of their respective studies (bradycardia, hypotension, convulsions, and sinus arrest). Analysis of the available information for these events leads this reviewer to find a probable causal relationship between these adverse events (with the possible exception of the convulsion) and dexmedetomidine as a direct reflection of the  $\alpha_2$  effects of that agent.

Three of the subjects in the non-Abbott-sponsored studies experienced serious adverse events during the course of their respective studies. Analysis of the available information for these subjects leads this reviewer to find a probable causal relationship between two of the adverse events (sinus arrest upon IV administration of the drug and allergic reaction upon transdermal application of the drug) and dexmedetomidine. The third adverse event, fainting, occurred upon placement of an intravenous cannula prior to receipt of the agent and is not temporally related to the study drug.

### Phase II/III

There were 1337 subjects in Abbott-sponsored studies and 1315 subjects in non-Abbott-sponsored studies exposed to dexmedetomidine during Phase II/III trials (ISS Supplement, Tables 2.1.1 – 2.3.3.2, p. 62-114). One hundred twenty-two of the 1337 (9%) dexmedetomidine-treated subjects in the Abbott-sponsored Phase II/III continuous infusion studies experienced at least one serious adverse event. Sixty-three of the 576 (11%) dexmedetomidine-treated subjects in the Abbott-sponsored Phase II/III continuous infusion ICU studies experienced at least one serious adverse event. A similar proportion of randomized dexmedetomidine- (9%, 102/1148) and placebo- (10%, 79/817) treated patients experienced at least one serious adverse event in these studies. In the non-Abbott-sponsored studies, 31 of the 1315 (2.4%) dexmedetomidine- treated subjects experienced at least one serious adverse event. (ISS, Vol. 1.301, pp. 55, 115.)

In the Abbott-sponsored ICU continuous sedation studies, the severe treatment emergent adverse events of hypotension (4%), hypertension (2%), and bradycardia (2%) were experienced by a higher proportion of randomized dexmedetomidine-treated patients compared to placebo-treated patients (2%, 1%, and 0%, respectively). Conversely, severe, not otherwise specified hemorrhage was experienced by a higher proportion of placebo-treated patients (2%) compared to randomized dexmedetomidine-treated patients (1%). All other serious adverse events were experienced by <1% of randomized dexmedetomidine- and placebo-treated patients. (ISS, Vol. 1.301, p. 53.) Similar data is unavailable for the non-Abbott-sponsored studies.

The adverse events of hypotension, hypertension, and bradycardia, known pharmacological effects of alpha-2 agonists, were frequently reported among patients who received dexmedetomidine in the continuous infusion trials. In the Abbott studies, only 5% of the reports of bradycardia, 4% of the reports of hypotension, and 1% of the reports of hypertension were considered to be serious adverse events. Of these, only three reports of hypotension and one report of bradycardia resulted in premature discontinuation of study medication. (ISS, Vol. 1.301, p. 59.)

Many of the Phase II/III Abbott studies included patients with underlying cardiac conditions and were conducted during or after cardiac surgery. Although hypotension and bradycardia were among the most common serious adverse events in the Phase II/III continuous infusion studies, the incidence of serious adverse events of cardiac arrest and myocardial infarction were comparable among dexmedetomidine and placebo treated patients in these studies.

**Table 3. Treatment Emergent Serious Adverse Events - Cardiovascular Phase II/III Continuous Infusion Studies**

	Dexmedetomidine-Treated			Placebo		
	Abbott	Non-Abbott	All	Abbott	Non-Abbott	All
Number of Treated Patients	1337	366	1703	817	167	984
Hypotension	18 (1%)	2 (<1%)	20 (1%)	13 (2%)	NA	NA
Bradycardia	7 (<1%)	3 (<1%)	10 (<1%)	1 (1%)	NA	NA
Cardiac Arrest	8 (<1%)	2 (<1%)	10 (<1%)	4 (<1%)	0	4 (<1%)
Myocardial Infarction	13 (<1%)	8 (2%)	21 (1%)	10 (1%)	3 (2%)	13 (1%)

From Sponsor's Table 2.1.3.2, ISS Supplement, pp. 83-93, Table 42, ISS, Vol 1.301, pp. 115-120.

One of the concerns with a sedative medication such as dexmedetomidine is its depressant effect on the respiratory system. However, there was a notable lack of reported serious adverse events of respiratory depression. In fact, with the exception of hypoxia, the incidence was also low for any reported treatment emergent respiratory adverse event that might indicate respiratory depressant effects. The incidence of all specific treatment-emergent respiratory adverse events was similar between dexmedetomidine and placebo groups.

**Table 4 Treatment Emergent Respiratory Adverse Events Phase II/III Continuous Infusion Studies**

	Dexmedetomidine-Treated			Placebo		
	Abbott	Non-Abbott	All	Abbott	Non-Abbott	All
Number of Treated Patients	1337	366	1703	817	167	984
Patients with at least One Respiratory AE	138 (10%)	22 (6%)	160 (9%)	97 (12%)	12 (7%)	109 (11%)
Apnea	9 (<1%)	3 (1%)	12 (<1%)	2 (<1%)	2 (1%)	4 (<1%)
Atelectasis	13 (<1%)	4 (1%)	17 (<1%)	13 (2%)	0	13 (1%)
Dyspnea	9 (<1%)	4 (1%)	13 (<1%)	6 (<1%)	0	6 (<1%)
Hypoxia	58 (4%)	1 (<1%)	59 (3%)	36 (4%)	1 (<1%)	37 (4%)
Resp Depression	4 (<1%)	0	4 (<1%)	11 (1%)	0	11 (1%)
Resp Insufficiency	9 (<1%)	0	9 (<1%)	6 (<1%)	1 (<1%)	7 (<1%)

From Sponsor's Table 2.1.3.2, ISS Supplement, pp. 83-93.

After a thorough review of all available data provided by the sponsor pertaining to serious adverse events in Abbott- and non-Abbott-sponsored trials, this reviewer concludes that the events noted in a higher proportion of dexmedetomidine-treated patients than placebo-treated patients appear to be an expected part of this agent's pharmacological action and not a result of a toxic side effect.

However, it should be noted that, according to the sponsor, "in the dexmedetomidine clinical program, the reporting of adverse events was based on clinical judgement rather than [on] predetermined criteria. Vital sign data may not have been recorded in the case report form at the time of the adverse event." (ISS, Vol. 1.301, p.59.). It should also be noted that serious adverse events were reported for subjects or patients to the clinical database and consequently to the overall safety database only for those events that occurred within 24 hours (48 hours for Study DEX 95-004) of participation in an Abbott-sponsored study. Serious adverse events reported up to 30 days were to have been included in the company's proprietary SAGE database. (ISS Vol. 1.301, p. 94). This database was reported in addition to the NDA database and an effort was made to reconcile any inconsistencies between the existing numbers. Consequently, inaccuracies in both the identification of serious adverse events and the total numbers of events reported for each study are a possibility.

### ***PART III - DEATHS - ADDITIONAL INFORMATION***

As reported in the Medical Officer Review of the NDA and the First Addendum to this review, there were no deaths during the Phase I studies. There were 13 dexmedetomidine deaths and 8 placebo deaths during the Phase II/III studies. These totals were based on data supplied by the sponsor in the Integrated Summary of Safety and the Integrated Summary of Safety Supplement.

The sponsor provided additional information on two dexmedetomidine deaths that had occurred in two ongoing and blinded Phase II studies cited in the 120-day safety update. These deaths were both reviewed in the First Addendum to the NDA Medical Officer Review.

A comparison has been performed of data submitted to the dexmedetomidine IND Annual Report dated 24 March 1999 and that submitted to the original submission and the 120-day safety update, specifically targeting number of deaths per study. Several discrepancies were noted between the NDA safety database and the Annual Report safety database. Nine additional deaths were reported to the IND (one dexmedetomidine-exposed subject, three placebo subjects, and five subjects with unclassified treatment group assignments) that were not listed in the NDA safety database. These discrepancies are outlined in the following table.

**Table 5**      **Discrepancies in Numbers of Deaths\***  
**Annual Report 31Jan 98 to 31Jan99 vs. NDA**

<i>Study #</i>	<i>Patient #</i>	<i>Treatment Group</i>	<i>In NDA Safety Database</i>	<i>In Mar 99 Annual Report</i>
97-245	1001	Placebo	No	Yes
97-245	10401	Placebo	No	Yes
97-245	? CS	?	No	Yes
97-245	105@	?	No	Yes
97-245	6301@	?	No	Yes
97-246	11601	Dexmedetomidine	No	Yes
97-246	704@	?	No	Yes
97-246	12406	Placebo	No	Yes
3005003	901@	?	No	Yes

\*Not included in NDA death listings in multiple Tables 2.1.4.14, Vol. 302-303.  
 @ Not in randomization schedule or any other line item report in NDA

The sponsor was asked to submit clarification and explanations for these discrepancies. A summary of this information follows:

In an October 1, 1999 written communication the sponsor reiterates their practice of maintaining their own centralized database for tracking serious adverse events and references Section 11 of the Integrated Summary of Safety in the NDA as follows:

“Abbott Laboratories’ maintains a centralized database of serious adverse global events (SAGE). This database includes all serious adverse events reported for subjects/patients from the time informed consent is signed to at least 30 days after participation in an Abbott-sponsored study.

Serious adverse events reported for subjects/patients within 24 hours (48 hours for Study DEX-95-004) of participation in an Abbott-sponsored dexmedetomidine study were to have been included in the clinical database for the specific study and consequently in the overall safety database, in addition to their inclusion in the SAGE database. Serious adverse events reported for subjects/patients 24 hours (48 hours for Study DEX-95-004) after participation up to 30 days in an Abbott-sponsored dexmedetomidine study were to have been included in the SAGE database, but may not have been included in the clinical database for the specific study or in the overall safety database.

In order to accurately reflect the number of serious adverse events reported during the Abbott-sponsored dexmedetomidine clinical program, a reconciliation of the overall safety database and the SAGE database was performed (presented in Section 11 of the ISS, Tables 35 and 36).”

The sponsor also provided explanatory information for each subject referenced in Table 3 above.

- **Study 3005003**, Patient #901 – this patient was a placebo group patient and died one month after study completion; sponsor stated that the information was submitted as part of NDA-21-038, Vol. 541. P. 8/10-237-263.

*Reviewer Comment: The information was verified as present and part of a short study synopsis of non-Abbott-sponsored Phase III studies.*

- **Study 97-245, Patients 105, 6301; Study 97-246, Patient #704** – sponsor states that these patients died intraoperatively and never received study drug; patients were never considered part of the study because they never entered the ICU and received a study drug; therefore they were not included in the safety data base nor were they in the clinical study reports

*Reviewer Comment: Patients were apparently assigned a study number prior to entering the operating room or at some time during the surgical procedure, thus appearing as a patient # in the Annual Report Death tabulation, and were then never randomized and enrolled in the study to begin the protocol treatment course. There are no independent means to verify this information. Sponsor has declined to provide patient information because subjects are not considered part of the study.*

- **Study 97-245, Patient #1001, 10401; Study 97-246, Patient #12406** – all three patients received placebo but all died at least five days after the end of study drug infusion (5, 12, and 35 days, respectively). According to the sponsor, "because these three deaths occurred more than 24 hours after completion of the study, they were not included in the NDA safety database." They were included in the "SAGE database and in narratives, which appeared in Appendix B of the ISS Vol 301, p. 8/10-239-162". (October 1, 1999 Sponsor letter, p. 2, para. 2)

*Reviewer Comment: The sponsor's information of inclusion is verified – the patients are included in the SAGE database and in the Appendix B narratives. However, the sponsor's explanation of lack of inclusion in the NDA database is confusing. Other placebo deaths in these same studies, occurring 10, 18, and 20 days after completion of the study, have been included in the NDA database. It would seem a more valid comparison to placebo effects to assign a cutoff date rather than to randomly include or exclude as this appears.*

- **Study 97-246, Patient #11601** – this patient received dexmedetomidine and died 5 days after study completion. According to the sponsor, "since the death occurred more than 24 hours after study completion, this patient was not included in the clinical study database. It would appear, however, that this patient was inadvertently omitted from Appendix B of the ISS." (October 1, 1999 Sponsor letter, p. 2, para. 3)

*Reviewer Comment: This patient received a dexmedetomidine infusion, was reported as a Serious Adverse Event (cardiac arrest - unrelated) to the NDA and was discontinued from the study; the patient subsequently died five days later. The Case Report Form for this patient was reviewed and is summarized below along with this reviewer's comments and conclusions about the events.*

*The subject was a 73 year old male with a history of hypertension and lung cancer who underwent a right pneumonectomy. He entered the dexmedetomidine ICU continuous infusion study on July 22, 1998. He received an infusion of dexmedetomidine (at constantly decreasing doses) for a total of seven hours, beginning at 15:02, during which time his systemic blood pressures ranged 10-40% below his admitting pre-infusion values. An initial adverse event report for "hypotension" was filed at 15:12 describing the event as "continuous", "moderate" in intensity, "probably" related to the study drug and stating that the drug was decreased, fluids were given, and the Trendelenberg position was employed.*

*A second adverse event report for "hypotension" was filed at 21:45 describing the event as "continuous", "moderate" in intensity, and "possibly" related. "Life-threatening" event and treatment with "dopamine" are also listed on this form but have been cross-out and the deletion is initialed. The last blood pressure recorded on the vital sign chart is for 22:00 - 83/48. At 22:10 a Dopamine infusion was started for "hypotension", the dexmedetomidine infusion was stopped at 22:22, and atropine and adrenaline were given shortly thereafter for "cardiac arrest".*

*The third adverse event report for "cardiac arrest - collapsus" was filed at 22:22 describing the event as "continuous", "severe" in intensity, and "probably not" related to the study drug infusion. The explanation for the event was "poor cardiac function - myocardial hypersensitivity to dopamine". The patient was revived from this episode of cardiac arrest; however, he was discontinued from the study and listed as a discontinuation secondary to an unrelated adverse event. The subject subsequently died 5 days later and the sponsor has provided no further information about the remainder of his hospital course.*

*This reviewer disagrees with the assessment of the investigator that this serious adverse event "cardiac arrest" was "unrelated" to the infusion of dexmedetomidine. The information provided in the Case Report Form demonstrates a temporal relationship between the onset of hypotension and the start of the infusion of this agent. The infusion was maintained at the lower end of the titratable range throughout the treatment period and two adverse event reports that were deemed related to the dexmedetomidine infusion were filed during this time of hypotension. In the space of a couple of minutes dopamine was started, the dexmedetomidine infusion was discontinued, and a cardiac arrest occurred. The investigator states that the cardiac arrest was due to a myocardial sensitivity to dopamine and not to the effects of dexmedetomidine. However, from the information provided, this reviewer is unable to reach that same conclusion. The hypotensive effects of dexmedetomidine may have played a role in this cardiac event - there is not enough information to*

*confirm or deny this possibility. Furthermore, if the cardiac event was a factor contributing to the patient's ultimate demise five days later, it is not possible to confirm or deny dexmedetomidine's role in that death.*

The summarization of serious adverse events and deaths in the dexmedetomidine clinical studies program has been a somewhat difficult endeavor because of three major but inter-related factors:

- With one exception, all clinical protocols were devised to require reporting of serious adverse events and deaths for only 24 hours from the time the infusion of the study drug was discontinued. With the exception of general patient satisfaction surveys in a few studies, no protocol-driven follow-up assessments were performed. Therefore, delayed reactions or longer-term effects of the drug were not recorded or discovered. It was the responsibility of the individual investigator to report to the sponsor any serious adverse events or deaths that occurred outside of this 24-hour time period. From the appearance of the data submitted, it would seem that this responsibility was not equally shared by all investigators.
- In the original NDA submission, the sponsor presented safety data tabulated in an NDA Clinical Trial Database" (CTDB) or overall safety database, including data for subjects reported per protocol (within 24/48 hours), and also safety data tabulated in their proprietary SAGE (Serious Adverse Global Events) database. This second database included all data reported to Abbott on patients in Abbott-sponsored studies from the time informed consent was signed to at least 30 days after participation in the study. Information included in the CTDB was not necessarily included in the SAGE database and vice versa although tables were constructed in an attempt to perform a reconciliation of the differences and to present a sum total of serious adverse events. (Tables 35, 36, ISS, Vol. 1.301, p. 8/10-239-106-119.). The sponsor also included short narratives of the patients who had been included in the SAGE database but not in the NDA Clinical Trial Database and presented these in Appendix B (ISS, Vol 1.301, p. 8/10-239-162). It is sometimes difficult to determine to which of these three databases the sponsor is referring when they are determining an incidence for a certain event or comparing with placebo.
- In their final analysis, the sponsor apparently follows no set guidelines for inclusion of deaths and serious adverse events from time of study drug infusion. They have not followed a 24-hour protocol-defined cut-off as they previously specified nor have they allowed a full 30-day reporting period as their SAGE database specifies. Although they have stated that the above referenced placebo deaths should not be included (see explanation under *Study 97-245, Patient #1001, 10401; Study 97-246, Patient #12406* above), they have included other deaths occurring up to 20 days after end of dexmedetomidine infusion.

The random inclusion and exclusion of serious adverse events and deaths, the reliance on sponsor-driven rather than protocol-driven event reporting, and the confusing state of the safety databases have confounded the issue of determining the actual number of deaths in the dexmedetomidine clinical studies. However, if all additional deaths in Table 5 are included, with the exception of the subjects who expired intraoperatively, the number of deaths can be summarized as in the table below.

**Table 6: Deaths in Dexmedetomidine Clinical Studies**

	Treatment	
	<i>Dexmedetomidine</i>	<i>Placebo</i>
Phase I Abbott	0	0
Phase II/III Abbott	15	11
<b>Total</b>	<b>16</b>	<b>12</b>

#### SUMMARY:

After review of all supplemental information provided by the sponsor (see listing below), the safety profile of dexmedetomidine remains consistent with that reported in the Medical Officer's Review of the original NDA submission and with that in the first addendum to this review. Dexmedetomidine is reasonably safe for its intended use.

Information accessed and analyzed for this review:

- Original NDA submission – ISS, Vols. 1. 301-1.303
- Amendment to NDA (8-17-99) – overview ISS supplement, AE summaries of Japanese studies, statistical summary tables
- Amendment to NDA (10-5-99 - CRF's for deaths as requested
- Amendment to NDA (10-01-99) – explanation of data differences between NDA and IND Annual Report submissions, explanation of SAGE and clinical study safety databases
- Amendment to NDA (10-8-99) – table of deaths in dexmedetomidine and placebo groups for clinical study program to date

- Amendment to NDA (10-19-99) – sponsor's proposal for extent of exposure graphic display
- Amendment to NDA (10-27-99) – extent of exposure charts
- Annual Progress Report to ~~the Division~~ on June 26, 1999 – serial #336, for period Jan 31, 1998 to Jan 31, 1999

ISI  
Patricia Hartwell, MD MBA  
Medical Officer

CC: Division File  
Original NDA #21-038  
HFD-170 Patricia Hartwell, MD MBA  
HFD-170 R.A. Rappaport, MD  
HFD-170 Project Manager: Susmita Samanta

**APPEARS THIS WAY  
ON ORIGINAL**

NDA: #21-038

NAME: Dexmedetomidine HCL for Infusion

SPONSOR: Abbott Laboratories

REVIEW DATE: 09-13-99

TYPE OF REVIEW: Addendum to NDA

REVIEWER: Patricia Hartwell, MD MBA

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**ADDENDUM TO MEDICAL OFFICER REVIEW**

**PART I - ADDITIONAL 120-DAY SAFETY UPDATE INFORMATION**

The sponsor has provided additional information on deaths, discontinuations, and serious adverse events in the Phase I and Phase II studies that were cited in the 120-day safety update of the original NDA review. This information is summarized below.

**DEATHS:**

Phase I

There have been no deaths reported in the three studies included in this update.

Phase II

*Study W98-263 (Subject 104)*

- A 79-year-old female patient with cardiac failure, chronic renal failure, and respiratory insufficiency was admitted to the ICU following a myocardial infarction and cardiac arrest. She was entered into an ongoing double-blind continuous infusion study. She suffered 6 serious adverse events including two episodes of hypotension and bradycardia (4 events) that were possibly related to administration of the study drug. The infusion was continued for a total of 18 hours until the decision was made to withdraw all supportive care. At this time the infusion of dexmedetomidine and all other medications were discontinued and the patient succumbed to her multi-organ failure shortly thereafter. Although it appears from the available information that the patient's ultimate demise was a result of her multi-organ failure, this reviewer

### PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

<b>NDA/BLA Number:</b>	<u>21038</u>	<b>Trade Name:</b>	<u>100MCG/ML I</u>
<b>Supplement Number:</b>		<b>Generic Name:</b>	<u>DEXMEDETOMIDINE HCL</u>
<b>Supplement Type:</b>		<b>Dosage Form:</b>	<u>INJ</u>
<b>Regulatory Action:</b>	<u>PN</u>	<b>Proposed Indication:</b>	<u>ICU sedation for patients 18 years and above</u>

**ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?**

NO, No waiver and no pediatric data

**What are the INTENDED Pediatric Age Groups for this submission?**

NeoNates (0-30 Days )     Children (25 Months-12 years)  
 Infants (1-24 Months)     Adolescents (13-16 Years)

**Label Adequacy**        Inadequate for ALL pediatric age groups  
**Formulation Status**  
**Studies Needed**  
**Study Status**

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

**COMMENTS:**

The agency has not not discussed pediatric studies with the sponsor yet. The Pediatric Rule paragraph will be in the action letter. 12/7/99

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, SUSMITA SAMANTA

Signature

SS

Date

12-7-99