U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 21-038 S021 & S022
Drug Name:	Precedex
Indication(s):	Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting
Applicant:	Hospira, Inc.
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Biometrics Division:	II
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Keywords:	NDA review, clinical studies, pediatric written request

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1. EXECUTIVE SUMMARY

Hospira has submitted a supplement for Precedex (dexmedetomidine) in response to a Pediatric Written Request (PWR) for the [redacted (b) (4)]. Precedex was approved in 1999 for adults as an intravenous infusion. The applicant submitted three efficacy studies to fulfill the requirement of the PWR [redacted (b) (4)]. Based on my review of the efficacy studies, I concluded that the applicant has responded fairly to the PWR. [redacted (b) (4)]

The PWR specified that the efficacy studies will be randomized, assessor-blinded and dose-controlled multicenter trials. A sufficient number of patients to provide a power of at least 80% to detect a statistically significant difference in the primary efficacy endpoint must complete the studies. Efficacy will be evaluated based on the percentage of patients who do not require rescue midazolam sedation using a validated, age-appropriate clinical sedation scale. A separate open-label study will be conducted for the 28 weeks gestational age to <1 month chronological age group.

Study DEX-08-05 was a randomized, double-blind, multicenter, and dose-controlled study evaluating the safety and efficacy of Precedex in pediatric subjects aged 1 month through 17 years old who required sedation in an intensive care setting for up to 24 hours. A total of 175 subjects were randomized equally to either a low dose or a high dose treatment group. Within each treatment group, the drug infusion rate could be titrated up to the maximum before administering the rescue midazolam. The primary efficacy variable was the percentage of subjects that did not require rescue midazolam for sedation based on achieving and maintaining a target sedation range while intubated. Approximately 45% of the subjects in the low dose group and 55% of the subjects in the high dose group did not require rescue midazolam for sedation. However, the difference was not statistically significant. The two dose groups were also similar in terms of the secondary efficacy endpoints. Even though Study DEX-08-5 was a dose-controlled study, there was an overlap of the dose ranges of the two treatment groups, which could have contributed the failure of the study to show dose response.

Study DEX-09-08 and Study DEX-11-06 were open-label and non-randomized studies conducted in neonates in the age range from 28 weeks gestational age to <1 month chronological age. Study DEX-09-08 and Study DEX-11-06 enrolled 42 subjects in total and studied three dose levels of Precedex. The efficacy endpoints were summarized in descriptive statistics. There were no meaningful differences in the percentages of subjects who required rescue midazolam among the three dose levels. Based on the study report, the subjects treated with the highest dose of Precedex even had numerically higher percent of the subjects who required rescue midazolam.

2. INTRODUCTION

2.1 Overview

Precedex (dexmedetomidine) was approved in 1999 for the sedation of initially intubated and mechanically ventilated adult patients during treatment in an intensive care setting for up to 24 hours. In 2008, Precedex was also approved for adults during non-intubated sedation. The current submission is to fulfill the Pediatric Written Request (PWR) (b) (4) (b) (4)

The PWR was originally issued in 2007. Thereafter, the division and the applicant have discussed revisions of the PWR on multiple occasions. The latest version of the PWR was Amendment #2 issued in 2011. The applicant stated that the studies (b) (4) were conducted in accordance with PWR Amendment #2, with study subjects spanning the age range from 28 weeks gestational age to < 17 years of age.

The PWR Amendment #2 specified the requirements for the efficacy and safety as well as pharmacokinetic studies. The following is an excerpt from the PWR Amendment #2 regarding efficacy and safety studies:

> These studies will be randomized, assessor-blinded, dose-controlled, multicenter trials based upon the dose-ranging findings of the initial pharmacokinetic studies. A separate open-label study will be conducted for the 28 weeks gestational age to <1 month chronological age group. Efficacy will be evaluated based on the percentage of patients who do not require rescue midazolam sedation using a validated, age-appropriate clinical sedation scale. The study population will require sedation for mechanical ventilation for less than 24 hours. The overall study population must encompass a broad range of underlying surgical and medical conditions that require sedation for mechanical ventilation. The protocol must include dosing guidelines that are appropriate to the patient's underlying condition as well as their age. For example, sedation dosing requirements in patients recovering from burn injury are likely to be higher than in patients following intracranial or heart surgery. Further PK data may be collected in the efficacy and safety studies to broaden an understanding of the pharmacokinetic variables and the understanding between pharmacokinetic variables and safety and efficacy endpoints.

The PWR requested that the primary efficacy endpoint should be the percentage of patients who didn't require rescue midazolam for sedation. A sufficient number of patients to provide a power of at least 80% to detect a statistically significant difference in the primary efficacy endpoint must complete the studies. Pediatric patients must be approximately evenly distributed between

genders and must be approximately equally distributed across the specified age groups and within the age groups.

The PWR specified the following age groups:

- ≥ 28 weeks gestational age to <1 month chronological age;
- 1 month to < 6 months;
- 6 months to < 12 months;
- 12 months to < 24 months;
- 2 years to < 6 years;
- 6 years to ≤ 16 years.

The applicant submitted three efficacy studies and three pharmacokinetic/pharmacodynamic (PK/PD) studies (b) (4). In all six studies, Precedex was administered as an intravenous (IV) infusion with or without a loading dose over a period of 10 to 20 minutes followed by a maintenance dose over a period of 6 to 24 hours. Among the three efficacy studies, Study DEX-08-05 was a randomized, double-blind, and dose-controlled study enrolling 175 subjects aged 1 month through 17 years old. The other two efficacy studies, Study DEX-09-08 and Study DEX-11-06 were open-label and non-randomized studies for neonate ≥ 28 weeks to ≤ 44 weeks gestational age. Study DEX-09-08 and Study DEX-11-06 enrolled 42 neonates in total. The statistical review focused on Study DEX-11-06. Findings from Study DEX-09-08 and Study DEX-11-06 were briefly summarized.

2.2 Data Sources

The datasets can be found at \\Cdsesub1\evsprod\NDA021038\0021\m5\datasets.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Some datasets in the initial submission were empty. The applicant submitted additional datasets per request from the division.

3.2 Evaluation of Efficacy

3.2.1 Study DEX-08-05

3.2.1.1 Study Design and Endpoints

Study DEX-08-05 was a Phase III, randomized, double-blind, multicenter, and dose-controlled study evaluating the safety and efficacy of Precedex in initially intubated and mechanically ventilated pediatric subjects in the pediatric intensive care setting. The pediatric subjects were aged 1 month through 17 years old and required sedation in an intensive care setting for up to 24 hours.

Subjects were anticipated to require a minimum of 6 hours of continuous intravenous sedation.

Eligible subjects were randomized equally into either the low-dose or high-dose Precedex treatment group. The randomization was stratified according to whether the subject had undergone cardiopulmonary bypass (CPB). Subjects with CPB were administered lower dose of the study drug in comparison to subjects without CPB as shown in Table 1. Subjects received an optional loading dose over 10 to 20 minutes and a maintenance dose for up to 24 hours. For both treatment groups, the maintenance dose could be titrated both up and down to achieve the desired level of sedation. Sedation level was assessed using the University of Michigan Sedation Scale (Table 2). When additional sedation was deemed necessary, the infusion rate was titrated upwards every 3 to 4 minutes. The need for rescue midazolam (MDZ) administration was reassessed thereafter. Fentanyl or morphine could be administered as needed for treatment of pain after the dose of Precedex was first titrated upwards. Subjects who were at maximum allowable titration of study drug and requiring more than fore rescue MDZ doses per hour were considered treatment failures and discontinued from the study.

Table 1: Loading Dose and Maintenance Dose Range – StudyDEX-08-05

	Low Dose		High Dose	
Diagnosis	**Loading dose (mcg/kg)**	**Maintenance dose range (mcg/kg/hr)**	**Loading dose (mcg/kg)**	**Maintenance dose range (mcg/kg/hr)**
Post cardiopulmonary bypass	0.2	0.025 – 0.5	0.5	0.1 – 0.7
All other diagnoses	0.3	0.05 – 0.5	0.6	0.2 – 1.4

Table 2: University of Michigan Sedation Scale (UMSS)

Clinical Score	Level of Sedation
0	Awake/Alert
1	Minimally sedated: tired/sleepy, appropriate response to verbal conversation and/or sounds
2	Moderately sedated: somnolent/sleeping, easily aroused with light tactile stimulation
3	Deeply sedated: deep sleep, arousable only with significant physical stimulation
4	Unarousable

The primary efficacy variable was the percentage of subjects that did not require rescue MDZ for sedation based on achieving and maintaining a target University of Michigan Sedation Scale (UMSS) range of 1 to 3 while intubated. The secondary efficacy variables included absolute time and percentage of time a subject was in a UMSS range of 1 to 3, total amount of rescue required for sedation, and time to first dose of rescue for sedation and analgesia.

3.2.1.2 Statistical Methodologies

The primary efficacy variable was analyzed using a chi-square test with continuity correction. The primary analysis population was the applicant defined efficacy evaluable (EE) population

which included all subjects who received drug infusion for at least 6 hours. The total amount of rescue, the absolute time and percentage of time that a subject was within the target sedation range were analyzed using Wilcoxon test. The time to first rescue was analyzed using a log-rank test.

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 175 subjects were randomized, 89 to the low dose and 86 to the high dose groups. The number and percentage of subjects by the age group as specified in the PWR are summarized in Table 3 below. There was one patient aged less than 1 month old. Table 4 shows the subject disposition with percentages based on all randomized subjects. About 13% of the subjects in the low dose and 12% of the subjects in the high dose groups discontinued the study early according to the applicant's study report. The most common reason for early discontinuation in both groups was lost to follow-up. A subject was deemed lost to follow-up when the post-dose Day 28 phone call was not completed.

Table 3: Number (%) of Subjects by Age Group – Study DEX-08-05

	Low Dose	High Dose
Randomized	89	86
Age group		
< 1 month	1 (1%)	
1 month to <6 months	31 (34%)	24 (28%)
6 months to <12 months	15 (17%)	14 (16%)
12 months to <24 months	17 (19%)	22 (26%)
2 years to <6 years	15 (17%)	13 (15%)
6 years to 16 years	11 (12%)	13 (15%)

Source: Clinical study report.

Table 4: Subject Disposition – Study DEX-08-05

	Low Dose	High Dose
Randomized	89	86
Subjects who completed the study	77 (87%)	76 (88%)
Discontinued study early	12 (13%)	10 (12%)
Reason for Study discontinuation		
Adverse event	2 (2%)	1 (1%)
Lost to follow-up	6 (7%)	7 (8%)
Physician reason	2 (2%)	1 (1%)
Other:	2 (2%)	1 (1%)

Source: Clinical study report.

Table 5 presents the summary of the status of the study drug infusion. There were approximately 96% of the subjects in the low dose group and 92% of those in the high dose group completed the drug infusion respectively. About 5% of the subjects in the high dose group discontinued the study drug due to adverse events.

Table 5: Study Drug Completion – Study DEX-08-05

	Low Dose	High Dose
Randomized	89	86
Received study drug infusion for at least 6 hours	83 (93%)	81 (94%)
Completed drug infusion	85 (96%)	79 (92%)
Discontinued study drug early	4 (4%)	7 (8%)
Reason for drug discontinuation		
Adverse event	0	4 (5%)
Lack of efficacy	1 (1%)	2 (2%)
Physician reason	0	1 (1%)
Require deeper sedation	1 (1%)	0
Other	2 (2%)	0

The demographic and baseline characteristics were similar between the two treatment groups. A summary of selected demographic and baseline characteristics is provided in Table 6. The majority of the subjects were Caucasian (72% in both groups). Approximately 60% of the subjects in the low dose group and 56% the subjects in the high dose group were female respectively.

Table 6: Demographics and Baseline Characteristics – Study DEX-08-05

	Low Dose N=89	High Dose N=86
Mean age (SD)	2 (3)	3 (4)
Mean weight (SD) (kg)	13 (16)	14 (14)
Mean height (SD) (cm)	65 (10)	66 (10)
Gender, n (%)		
Male	53 (60%)	48 (56%)
Female	36 (40%)	38 (44%)
Race, n(%)		
Black	14 (16%)	14 (16%)
Caucasian	64 (72%)	62 (72%)
Other	11 (12%)	10 (12%)

Source: Clinical study report; SD: standard deviation.

3.2.1.4 Results and Conclusions

I replicated the applicant's results for the primary efficacy analyses. Table 7 includes both the analysis results from the primary analysis, and from the same analysis model applied to a different analysis population. For both analyses, the subgroup results by the underlying conditions are displayed. The high dose group had higher percent of subjects who did not require rescue MDZ for sedation within the target range. However, the difference was not statistically significant. It appears that the greatest difference between the two groups was in subjects who underwent post cardiopulmonary bypass. The applicant's efficacy evaluable population only included subjects who received study drug infusion for at least 6 hours. The analyses results based on all randomized subjects (ITT) are similar.

Table 7: Primary Efficacy Results – Study DEX-08-05

Population		Low Dose	High Dose	P-value
Efficacy Evaluable	Total	N=83	N=81	
		37 (45%)	**44 (54%)**	**0.3**
Underlying conditions	Post cardiopulmonary bypass	N=33	N=34	
		9 (27%)	17 (50%)	0.1
	All other diagnoses	N=50	N=47	
		28 (56%)	27 (57%)	> 0.9
All randomized	Total	N=89	N=86	
		41 (46%)	**47(55%)**	**0.3**
Underlying conditions	Post cardiopulmonary bypass	N=36	N=37	
		11 (31%)	18 (49%)	0.2
	All other diagnoses	N=53	N=49	
		30 (57%)	29 (59%)	> 0.9

SD: standard deviation; CI: confidence interval; ITT: intention-to-treat.
Source: Clinical Study Report.

As the randomization was stratified by underlying surgical conditions, I conducted an additional analysis using Cochran-mantel-haenszel method stratified by subject's underlying condition. The additional analysis produced similar results to the primary analysis. Furthermore, I compared the percentages of subjects who not only did not require rescue MDZ for sedation but also completed the study drug infusion. Among all randomized subjects, there were 39 (44%) and 43 (50%) such subjects in the low dose and high dose groups respectively. The difference was also not statistically significant.

My analyses of the secondary efficacy endpoints yielded similar results to the applicant's. There were no statistical significant differences between the two treatment groups in the secondary efficacy endpoints such as percentage of time within the target sedation range, the total amount of rescue MDZ, and the time to first rescue for sedation and analgesia. Mean amount of rescue

MDZ, absolute time and percentage of time that subjects were in the target sedation range are summarized in Table 8 for the ITT population. The median percentage of time in the target range of sedation was 94% in the low dose group and 95% in the high dose group.

Table 8: Secondary Efficacy Results – Study DEX-08-05

Population	Endpoint	Low Dose	High Dose	P-value
All randomized		N=89	N=86	
	Median time in sedation (hour) #	17	16	0.7
	Percentage of time in sedation #	94%	95%	0.8
	Mean amount of rescue (mg)*	4	3	0.7
Underlying condition				
Post cardiopulmonary bypass	Median time in sedation (hour) #	15	12	0.2
	Percentage of time in sedation #	87%	93%	0.2
	Mean amount of rescue (mg)*	2	2	0.4
All other diagnosis	Median time in sedation (hour) #	19	20	0.7
	Percentage of time in sedation #	97%	99%	0.4
	Mean amount of rescue (mg)*	6	3	0.2

Source: Clincial study report.
*: among rescued subjects, p-value is based on Wilcoxon test with no multiplicity adjustment;
#: p-value for median time and percentga of time are based on median test with no multiplicity adjustment.

3.2.2 Study DEX-09-08 and Study DEX-11-06

3.2.2.1 Study Design and Endpoints

Study DEX-09-08 was an open-label, non-randomized, multicenter, safety, efficacy, and pharmacokinetics study of Precedex in neonates. The study population consisted of initially intubated and mechanically ventilated neonates ≥ 28 weeks to ≤ 44 weeks gestational age, who required sedation in an intensive care setting for a minimum of 6 hours. Subjects were divided into two groups by age: age group I consisted of premature neonates ≥ 28 weeks to < 36 weeks, and age group II consisted of term neonates ≥ 36 weeks through ≤ 44 weeks gestational age. Within each age group, there were three escalating dose levels. Each subject participated in one dose level only. The next dose level could not begin to enroll until all subjects had completed the previous dose level. Subjects were administered a loading infusion for 10 or 20 minutes followed by a maintenance infusion for up to 24 hours. Sedation/pain score was assessed using the Neonatal Pain, Agitation, and Sedation Scale (N-PASS). Rescue medication was administered as needed for sedation (midazolam) and pain (fentanyl or morphine) based on the N-PASS score. Rescue therapy was indicated when the total N-PASS score was greater than 3 at the discretion of the investigator. The study treatment and enrollment for each age group are shown in Table 9. According to the applicant, the study was discontinued early for non-safety related reason and did not enroll patients in age group I for dose level 3. To complement Study DEX-09-08, Study DEX-11-06 was conducted to enroll six neonates ≥ 28 weeks to < 36 weeks (age group I) for dose level 3.

Table 9: Treatment and Enrollment – Study DEX-09-08 and Study DEX-11-06

		Number of Subjects by Age group		Loading Dose	Maintenance infusion
Study	**Dose level**	**≥ 28 to < 36 weeks**	**≥ 36 to ≤ 45 weeks**	**(mcg/kg)**	**(mcg/kg/hr)**
DEX-09-08	1	6	8	0.05	0.05
	2	6	8	0.1	0.1
	3	0	8	0.2	0.2
DEX-11-06	3	6	0	0.2	0.2

The primary efficacy variable for both studies was the percentage of subjects that received rescue MDZ for sedation during infusion while intubated. Secondary efficacy endpoints included amount of rescue MDZ, absolute and percentage of time in target sedation range.

3.2.2.2 Statistical Methodologies

The efficacy variables were summarized for each dose level with descriptive statistics in the study reports. All subjects received drug infusion for at least 6 hours.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

There were no subjects who discontinued prematurely in Study DEX-09-08 or Study DEX-11-06. A summary of selected demographic and baseline characteristics by dose level and age group is provided in Table 10 for all subjects who received Precedex in the two studies. Of note, data for the subjects with gestational age ≥ 28 to < 36 weeks administered dose level 3 was from Study DEX-11-06. Overall, the majority of the subjects were Caucasian. At least 50% of the subjects in each age group within each dose level were male except for the age group II within dose level 1.

Table 10: Demographics and Baseline Characteristics – Study DEX-09-08 and Study DEX-11-06

	Dose Level 1		Dose Level 2		Dose Level 3	
	Age group I	Age group II	Age group I	Age group II	Age group I	Age group II
N	6	8	6	8	6*	8
Mean age (SD) (weeks)	30 (2)	38 (2)	33 (2)	39 (2)	33 (3)	39 (2)
Mean weight (SD) (kg)	1.4 (0.3)	3.4 (0.5)	1.7 (0.4)	3 (0.5)	1.9 (0.8)	3 (0.6)
Mean height (SD) (cm)	40 (2)	51 (3)	43 (2)	48 (3)	43 (5)	50 (3)
Gender, n (%)						
Male	4 (67%)	3 (38%)	3 (50%)	6 (75%)	4 (67%)	7 (88%)
Female	2 (33%)	5 (62%)	3 (50%)	2 (25%)	2 (33%)	1 (12%)
Race, n(%)						
Black	0	0	1	0	0	0
Caucasian	3 (50%)	7 (88%)	2 (33%)	8 (100%)	5 (83%)	6 (75%)
Other	3 (50%)	1 (12%)	3 (50%)	0	1 (17%)	2 (25%)

Source: Clinical study report; SD: standard deviation.
Age group I: ≥ 28 to < 36 weeks; Age group II: ≥ 36 to ≤ 45 weeks; *: From Study DEX-11-06.

3.2.2.4 Results and Conclusions

Table 11 presents the percentages of subjects who required rescue midazolam for sedation. No subjects of 28 through 36 weeks gestational age required rescue midazolam. Among subjects of 36 to 44 weeks gestational age, one subject in dose level 1, one subject in dose level 2 and two subjects in dose level 3 required rescue midazolam. Neither data from Study DEX-09-08 alone or in combination with Study DEX-11-06 suggested that subjects receiving a higher dose of Precedex were less likely to require rescue midazolam for sedation compared to subjects receiving a lower dose. The highest dose level even had numerically higher percent of subjects who requested rescue MDZ. There was also no dose response observed in the secondary efficacy endpoints. As shown in Table 12, median dose of midazolam used by subjects receiving rescue was 0.4 mg for dose level 1, 0.5 mg for dose level 2, and 1.1 mg for dose level 3. The median percent time spent in the target sedation range was at least 98% for both age groups at all dose levels.

Table 11: Percentage of Subjects Who Required Rescue MDZ – Study DEX-09-08 and Study DEX-11-06

Study	Age Group	Dose Level 1	Dose Level 2	Dose Level 3
DEX-09-08		N=14	N=14	N=8
	≥ 28 to < 36 weeks	0/6 (0%)	0/6 (0%)	
	≥ 36 to ≤ 45 weeks	1/8 (13%)	1/8 (13%)	2/8 (25%)
	all subjects	1/14 (7%)	1/14 (7%)	2/8 (25%)
DEX-11-06				N=6
	≥ 28 to < 36 weeks			0/6 (0%)
Two Studies Combined	all subjects	1/14 (7%)	1/14 (7%)	2/14 (14%)

Source: Clinical Study Report.

Table 12: Secondary Efficacy Results – Study DEX-09-08 and Study DEX-11-06

Endpoints	Age Group	Dose Level 1 N=14	Dose Level 2 N=14	Dose Level 3 N=14
Median dose of Rescue midazlom (mg) for subjects who received rescue				
	≥ 28 to < 36 weeks			
	≥ 36 to ≤ 45 weeks	0.4	0.5	1.1
	all subjects	0.4	0.5	1.1
Median percent of time in target sedation range				
	≥ 28 to < 36 weeks	98%	100%	100%
	≥ 36 to ≤ 45 weeks	98%	98%	98%
	all subjects	100%	100%	99%

Source: Clinical Study Report.

3.3 Evaluation of Safety

The evaluation of the safety data was conducted by Dr. Leah Crisafi. The reader is referred to Dr. Crisafi's review for detailed information regarding the adverse event profile.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The applicant conducted subgroup summaries by age groups, sex and race for the integrated datasets. I conducted subgroup summaries by age group, gender and race for the primary efficacy endpoint in Study DEX-08-05. Since Study DEX-09-08 and Study DEX-11-06 enrolled only 42 subjects in total, I did not conduct additional subgroup summaries.

4.1 Gender, Age and Race

Table 13 shows the subgroup summaries of the percentage of subjects who did not require rescue MDZ for sedation by age, gender, and race. The age groups are as defined in the PWR. It appears that the numerical differences between the dose groups were not consistently in the same direction across the subgroups. For example, for males, the high dose group had a higher percentage of subjects who did not require rescue. In contrast, for females, the low dose group worked better. This is not unexpected given that there was no significant difference between the dose groups among all the randomized subjects.

Table 13: Subgroup Summary – Study DEX-08-05

	Low Dose		High Dose	
Subgroup	N	n (%)	N	n (%)
All randomized	89	41 (46%)	86	47 (55%)
Age group				
< 1 month	1	1 (100%)		
1 month to <6 months	30	14 (47%)	24	17 (71%)
6 months to <12 months	15	5 (33%)	14	5 (36%)
12 months to <24 months	17	9 (53%)	22	10 (45%)
2 years to <6 years	15	3 (20%)	13	7 (54%)
6 years to 16 years	11	9 (82%)	13	8 (62%)
Gender				
Male	36	11 (31%)	38	26 (68%)
Female	53	30 (57%)	48	21 (44%)
Race				
Black	14	9 (64%)	14	9 (64%)
Caucasian	64	26 (41%)	62	33 (53%)
Other	11	6 (55%)	10	5 (50%)

4.2 Other Special/Subgroup Populations

For Study DEX-08-05, subgroup summaries by underlying surgery conditions for the primary efficacy endpoint and selected secondary endpoints are presented in previous section in Tables 7 and 8. No other special subgroup summaries were conducted.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The PWR requested that the efficacy of Precedex in pediatric populations should be demonstrated through randomized, assessor-blinded and dose-controlled studies. The pediatric subjects must be approximately evenly distributed between genders and must be approximately equally distributed across the specified age groups.

Study DEX-09-08 was the only randomized, double-blind and dose-controlled efficacy study. The applicant stated that the study was initially powered to detect a difference in the primary efficacy endpoint between the treatment groups. However, it failed to demonstrate a dose response. There was only numerical difference between the high dose and low dose groups. Both treatment groups had about 50% of the subjects who requested rescue MDZ. The applicant analyzed the primary efficacy endpoint among subjects who received infusion for at least six hours. The analyses based on all randomized subjects yielded similar results. I also conducted various exploratory analyses, none of which revealed a convincing dose response.

The following design issues could have contributed to the failure of the study. At first, although it was a dose-controlled study, the individual dose within each treatment group could be titrated up to be effective. As such, there was substantial overlap of the ranges of the dose administered for the treatment groups. Some subjects in the low dose group received greater amount of the study drug than some subjects in the high dose group. Second, the loading dose was optional with different duration at the discretion of the investigator, which might have increased the variability of clinical response among subjects. Third, the dosing strategy and efficacy assessments were the same for subjects with wide range of ages, which might not be appropriate.

There were also no observations suggesting a dose response of Precedex in neonates from the two open-label efficacy studies.

5.2 Collective Evidence

The efficacy studies failed to demonstrate a statistically significant difference in the percentages of subjects who required rescue MDZ for sedation between treatment groups. The secondary efficacy endpoints were also similar across different treatment groups. With lack of significant evidence of dose response, (b) (4)

(b) (4)

5.3 Conclusions and Recommendations

It appears that the applicant has responded fairly to the PWR requirement. However, there was lack of statistically significant evidence of dose response. (b) (4)

5.4 Labeling Recommendations

The applicant updated the label to include information for pediatric population. The texts in red below were added to the clinical study section of the label:

14 CLINICAL STUDIES

The safety and efficacy of Precedex has been evaluated in four randomized, double-blind, placebo-controlled multicenter clinical trials in 1185 adult patients. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

It appears that the applicant does not intend to describe the efficacy findings in the studies. (b) (4)

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