Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Cross-Discipline Team Leader and Division Director Summary Review for Regulatory Action

Date	December 16, 2022
From	Lisa Banta, MD; Renee Petit-Scott, MD; Alla Bazini, MD; Rigoberto Roca, MD
NDA# and Supplement#	021038, Supplement 028
Applicant	Hospira, Inc.
Date of Original Submission	August 28, 2015 (accepted October 21, 2015) Complete Response Letter issued August 19, 2016
Date of Complete Response Submission	June 17, 2022
PDUFA Goal Date	December 17, 2022
Proprietary Name	Precedex
Established or Proper Name	Dexmedetomidine Hydrochloride injection
Dosage Forms and Strengths	• 200 mcg/2 mL (100 mcg/mL) in a glass vial. To be used after dilution. • 80 mcg/20 mL (4 mcg/mL) in 0.9% Sodium Chloride Injection, in a glass vial. Ready to use.
Applicant Proposed Pediatric Indication	For sedation of non-intubated pediatric patients aged 1 month to 16 years prior to and during non-invasive procedures
Applicant Proposed Dosing Regimens	Initiation of Procedural Sedation: For pediatric patients (1 month to less than 2 years): a loading infusion of 1.5 mcg/kg over 10 minutes. For pediatric patients (2 to 16 years): a loading infusion of 2 mcg/kg over 10 minutes. A reduction in dosage should be considered if clinically indicated. Maintenance of Procedural Sedation: For pediatric patients (1 month to 16 years): the maintenance infusion is generally initiated at 1.5 mcg/kg/hour and titrated to achieve desired clinical effect with dosage ranging from 0.5 to 1.5 mcg/kg/hour. As clinically warranted, the maintenance dose should be titrated to individual patient clinical response.
Regulatory Action	Approval
Approved Dosing Regimens	Initiation of Sedation of Pediatric Patients During Non-invasive Procedures: • 1 month to less than 2 years: a loading infusion of 1.5 mcg/kg over 10 minutes • 2 to less than 18 years: a loading infusion of 2 mcg/kg over 10 minutes Consider a reduction in dosage if clinically indicated. Maintenance of Sedation of Pediatric Patients During Non-invasive Procedures: • 1 month to less than 18 years: the maintenance infusion is generally initiated at 1.5 mcg/kg/hour and titrated to achieve desired clinical effect with dosage ranging from 0.5 to 1.5 mcg/kg/hour. As clinically warranted, titrate the maintenance dose to individual patient clinical response.

Approved Indication	For sedation of non-intubated pediatric patients aged 1 month to less than 18 years prior to and during non-invasive procedures

OND Action Package includes reviews by the following:	
Clinical Pharmacology Review Team Pharmacometrics Review Team	Srikanth Nallani, PhD; Yun Xu, PhD Jie Liu, PhD; Atul Bhattaram, PhD
Pharmacology-Toxicology Review Team	Min Zhang, PhD; Newton Woo, PhD
Division of Biometrics I	Katherine Meaker, PhD; Sue-Jane Wang, PhD
Office of Product Quality Review Team	Daneli Lopez-Perez, PhD; Gupreet Gill-Sangha, PhD
Office of Scientific Investigations	John Lee, MD; Phillip Kronstein, MD; Jenn Sellers, MD, PhD
Division of Pediatrics and Maternal Health	Ramy Abdelrahman, MD; Mona Khurana, MD

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Precedex™ (dexmedetomidine hydrochloride) was initially approved in 1999 for sedation of intubated and mechanically ventilated (adult) patients in an intensive care unit (ICU) setting. An adult procedural sedation indication was approved in 2008, at which time a pediatric evaluation was required under the Pediatric Research Equity Act (PREA). The adult procedural sedation studies evaluated subjects undergoing elective surgery requiring monitored anesthesia care in combination with local or regional anesthesia (Study 2005-005) and subjects undergoing awake fiberoptic intubation using local anesthetic topicalization of the airway (Study 2005-006). On August 28, 2016, data from subjects undergoing one of a several of procedures in Study DEX-10-16 were submitted in Prior Approval Supplemental NDA (PAS, sNDA) 28 to support pediatric dosing. The PAS received a Complete Response (CR) letter on August 19, 2016, primarily due to the lack of adequate sedation (efficacy) for successful completion of the pediatric procedures evaluated.

On June 17, 2022, Hospira Inc. (Hospira) submitted this complete Class 2 sNDA resubmission proposing to add pediatric dosing information for procedural sedation to the prescribing information for Precedex. To support this sNDA, the Applicant submitted data from one study, Study C0801039, conducted in pediatric subjects from one month to 16 years of age undergoing MRI. Three dexmedetomidine (DEX) dose groups were evaluated in this study (designated low, middle, and high), with propofol rescue for inadequate sedation. No other sedative, anesthetic, or analgesic medications were permitted during the study. The primary efficacy endpoint was the percentage of subjects in the high-dose DEX group compared to the low-dose DEX group who did not require propofol rescue for successful completion of the MRI. Statistically significant differences favoring the high-dose DEX group were observed, with a p-value <0.001.

The data from the adult studies and from Study C0801039 indicate that dexmedetomidine is generally not an adequate sedative agent for invasive (painful) procedures, and that its true benefit is either as an adjunctive agent during invasive procedures or when administered during non-invasive procedures. While MRI is the radiological evaluation of choice for many soft tissue pathologies, it is sensitive to motion artifact, more so than CT imaging, such that even subtle patient movement can adversely impact the image, and result in the need for a repeat scan. In addition, an average duration of an MRI scan can be anywhere from 30 minutes to more than one hour. With few exceptions, children one month of age and older require sedation or general anesthesia for successful completion of the scan. Commonly administered sedative and anesthetic agents in this population include propofol, benzodiazepines, opioid analgesics, ketamine, dexmedetomidine, and inhalational anesthetic gases and nitrous oxide. Dexmedetomidine has several benefits over other agents particularly in the pediatric population including less risk of neurotoxicity based on nonclinical data, relatively short onset of action, relatively easy to titrate to desired clinical effect, safety and efficacy profiles well-described in published literature, can be used as a sole agent for relatively short procedures, less respiratory depression and hemodynamic instability

compared to other agents, no airway irritation, commonly administered with other sedative and anesthetic agents (although not explicitly evaluated in Study C0801039), and is not a scheduled substance under the Controlled Substances Act.

The most common and clinically relevant risks associated with dexmedetomidine administration are ECG and vital sign changes. Bradycardia, tachycardia, hypotension, hypertension, bradypnea, apnea, and hypoxia are all known to occur during or following administration of dexmedetomidine. Cardiac arrhythmias have also been observed including atrial fibrillation and ventricular arrhythmias. The adverse events most commonly reported during Study C0801039 were bradypnea, bradycardia, hypertension, and hypotension, and while the incidences of bradypnea, bradycardia, and hypertension were higher than those reported in the adult procedural sedation studies, the Division concludes that the benefit of dexmedetomidine outweighs these risks for the following six reasons.

First, the criteria used to determine a vital sign-related adverse event in Study C0801039 were based on the age-based cut-off values described in Fleming *et al*., (2011). These criteria define vital sign-related adverse events, specifically bradycardia and bradypnea, that appear to be more conservative than that used in other pediatric sedation studies and in the adult studies conducted to add a procedural sedation indication to the Precedex label.

Second, in the adult studies, and in published pediatric procedural sedation studies, the dexmedetomidine dosing regimen differed than that used in Study C0801039. Specifically, in the adult studies, the infusion of dexmedetomidine could be titrated based on clinical effect or the occurrence of adverse events. In Study C0801039, there were no dose-adjustments permitted, aside from treatment discontinuation. This suggests that the adult studies may have reported fewer vital sign-related adverse events if the dose was adjusted to prevent the occurrence of an adverse event.

Third, all adult subjects in Study 2005-006 received glycopyrrolate 0.1 mg i.v. prior to administration of the study drug. This pretreatment clearly would have impacted the number and severity of reported bradycardic events.

Fourth, the adverse event data summarized in Table 7 in the label includes treatment failures (subjects who received propofol rescue), which would have clearly impacted the incidence of reported adverse events. While the impact of propofol administration would likely be greater in the low- and middle-dose DEX groups given the higher proportion of subjects rescued with propofol in those treatment groups, there were 14 subjects in the high-dose DEX group who failed study drug treatment, and many of them experienced adverse events.

Fifth, the majority of vital sign-related adverse events were mild in severity. Only two subjects in the high-dose DEX group required anticholinergic treatment for bradycardia, and no subject in any dose group required airway intervention, including jaw thrust or insertion of a naso- or oropharyngeal airway, for bradypnea or respiratory depression.

And sixth, given the widespread off-label use of dexmedetomidine in the pediatric population, changes in measured hemodynamic parameters, particularly bradycardia, are anticipated, and therefore, generally quickly treated. An additional consideration is that Study C0801039 was a relatively small study, such that the percentage of a specific adverse event would likely appear high.

Therefore, the Division concludes that dexmedetomidine was shown to be effective in maintaining adequate sedation for pediatric subjects one month to 16 years of age undergoing MRI, and there do not appear to be any new risks associated with its use in pediatric patients that would preclude approval. Further, the data from Study C0801039 can be extrapolated to other non-invasive procedures, most likely other radiological or ultrasound procedures, such that the Applicant's proposed indication is acceptable. Because data from this study can be extrapolated to pediatric patients less than 18 years of age, the Division recommends the indication include patients in this age group.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pediatric patients require sedation or general anesthesia for completion of a variety of diagnostic and therapeutic procedures and surgeries. • Pediatric patients undergoing minimally invasive or non-invasive procedures also require sedation or general anesthesia, depending on age and type of procedure, due to the need for them to remain still throughout.	While exposure to sedative agents may be low in the general population, pediatric patients undergoing diagnostic and therapeutic procedures have a high likelihood of receiving a sedative or an anesthetic agent. The goals of adequate sedation during a non-invasive procedure for a pediatric patient include immobility, maintenance of spontaneous ventilation, rapid onset and recovery, and procedure success. Commonly performed non-invasive procedures in pediatric patients include radiological and ultrasound imaging, including transthoracic echocardiography (TTE). While closed reductions of orthopedic fractures and dental cleanings are considered non-invasive procedures, they are painful and could not be successfully performed without administration of additional agents.
Current Treatment Options	• Commonly administered i.v. agents used (in isolation or combination with other agents) for sedation of pediatric patients include benzodiazepines (e.g., midazolam), opioid analgesics (e.g., fentanyl), propofol, ketamine, and dexmedetomidine. However, only midazolam, ketamine, and methohexital (rarely used in clinical practice due to adverse event profile) are approved for pediatric procedural sedation. • Inhalational agents (e.g., sevoflurane, nitrous oxide) can be used for sedation in pediatric patients.	While only three sedative agents are approved for pediatric procedural sedation, propofol and dexmedetomidine are among the most commonly administered based on adverse event profiles and ease of access and administration. The reported adverse events associated with the approved products makes their use in clinical practice less desirable. Specifically, high doses of midazolam are required when used as a sole agent; ketamine is associated with a high incidence

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• For neonates less than one month of age, non-sedate feed and swaddle methods are commonly performed during non-invasive, non-painful procedures. • Pediatric patients who cannot complete the procedure under sedation can be administered a general anesthetic for successful completion, including propofol, ketamine, and/or inhalational agents.	of emergence reactions and nausea/vomiting; and methohexital is not recommended for prolonged administration due to cumulative effects. Additionally, based on nonclinical data, it appears there may be an increased risk of neurotoxicity in pediatric patients associated with administration of midazolam, ketamine, methohexital, and propofol.
Benefit	• The benefits of dexmedetomidine administration to pediatric patients undergoing non-invasive procedures include the following: ○ Juvenile animal data suggest a lower risk of pediatric neurotoxicity compared to other agents ○ Relatively short onset of action ○ Easily titratable to desired clinical effect ○ In general, predictable safety and efficacy profiles for all ages ○ Ideal sedative for relatively short (i.e., two hours or less) procedures ○ Less respiratory depression than observed following administration of propofol or opioid analgesics ○ No airway irritation ○ Can be used as a sole sedative agent ○ Commonly administered with other sedative or anesthetic agents, although not specifically evaluated in Study C0801039 ○ Not a scheduled substance under the Controlled Substances Act (less cumbersome disposal procedure)	There are several benefits of dexmedetomidine administration in pediatric patients undergoing non-invasive procedures. Because this drug has been used off-label for many years for a variety of indications, including pediatric procedural sedation, clinicians are familiar with the benefits and risks, and will often choose this drug over approved products (e.g., ketamine) based on adverse event profiles. The data from Study C0801039 demonstrate that dexmedetomidine is effective as a sole agent for sedation of pediatric subjects from one month to 16 years of age during MRI. The Division concludes that data from this study can be extrapolated to other non-invasive procedures, where dexmedetomidine can be administered as a sole sedative agent, and to patients less than 18 years of age. Approval of Precedex for pediatric sedation during non-invasive procedures will provide clinicians with an additional *approved* medication for use in this population, and the benefits and risks of its use in this population will now be described in labeling.
Risk and Risk Management	• The primary risks associated with administration of dexmedetomidine are changes in measured vital sign parameters, such as the following: ○ Bradycardia, tachycardia ○ Hypotension, hypertension ○ Bradypnea, apnea	As noted above, because dexmedetomidine has been widely used (off-label) in the pediatric population, the risks of administration are well known and well-described in the published literature. The risks can be serious, however, and include hemodynamic instability and cardiac arrhythmias.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	○ Hypoxia • ECG changes are also commonly reported, and can include the following: ○ Atrial fibrillation, other supraventricular arrhythmias ○ Ventricular arrhythmias, include ventricular tachycardia ○ Extrasystoles ○ Atrioventricular block ○ T wave inversion ○ QT prolongation • Additional risks associated with dexmedetomidine are the inability to reverse its effects with administration of an antidote, and prolonged recovery compared to other agents (e.g., propofol). • Based on the long history of clinical use of dexmedetomidine and the information included in the label, practitioners are generally prepared to adequately treat hemodynamic instability and abnormalities in the ECG. • Discontinuing administration is the first and best treatment option.	Risk mitigation strategies include administration by a trained anesthesia provider, adequate hemodynamic and cardiac monitoring, and immediate availability of emergency airway equipment and resuscitation medications. Additionally, discontinuation of treatment generally resolves the hemodynamic and cardiac abnormalities.

2. Background

Precedex™ (dexmedetomidine hydrochloride) is a selective α2-agonist and was initially approved on December 17, 1999, for sedation of intubated and mechanically ventilated (adult) patients during treatment in an intensive care unit (ICU) setting. A Pediatric Written Request (PWR) was issued on March 14, 2007, based on a request from the Applicant, "to obtain needed pediatric information," and the Applicant submitted data from four clinical studies in 124 mechanically ventilated pediatric patients ranging from 28 weeks gestational age to less than 17 years of age receiving dexmedetomidine infusions in the ICU (i.e., Study CHOP, DEX-11-01, DEX-08-01, and DEX-09-08) in PAS 21 and PAS 22 to fulfill the PWR. Both supplements were approved; however, due to concerns regarding the lack of efficacy, use of rescue sedation, and safety concerns (i.e., adverse event capture, possible hypotension signal), neither a pediatric indication nor recommended pediatric dosing were included in the label. Edits to Section 8.4 Pediatric Use were included. Refer to the Primary Clinical Review completed by Dr. Leah Crisafi (dated May 23, 2013), and the Division Director Summary Review completed by Dr. Rigoberto Roca (dated June 17, 2013) for additional information regarding the PWR and submitted supplements.

On October 17, 2008, Precedex was approved for sedation of non-intubated (adult) patients prior to and/or during surgical and other procedures based on the information submitted in Prior Approval Supplement (PAS) 10. With the approval of that sNDA, the following pediatric postmarketing requirement under the Pediatric Research Equity Act (PREA) was issued:

> 1772-1 Deferred pediatric study under PREA for the treatment of sedation of non-intubated patients prior to and/or during surgical and other procedures in pediatric patients 0 to 16 years of age.

The Applicant submitted PAS 28 to the NDA on August 28, 2015 (accepted on October 21, 2015, due to user fee delay), which included the results from Study DEX-10-16 and was intended to add pediatric dosing information to the label and fulfill PMR 1772-1. Study DEX-10-16 was an open-label study conducted in the U.S. in pediatric subjects undergoing a variety of procedures for which sedation is required for successful completion. Evaluated procedures included non-invasive diagnostic and therapeutic procedures (e.g., ultrasound, CT scan, MRI, cardiac catheterization, transthoracic echocardiography), minimally invasive diagnostic or therapeutic procedures performed under ultrasound or CT guidance (e.g., biopsies), and surgical procedures including small surgical procedures and dental procedures. The composite primary efficacy endpoint was the rate of success in sedation defined as the percent of subjects who met the following criteria:

- Adequately sedated at least 80% of the time (based on the University of Michigan Sedation Score and the Neonatal Pain, Agitation, and Sedation Scale scoring)
- No rescue sedation
- No artificial ventilation or hemodynamic intervention

The study failed on its primary endpoint, with only two of the 78 subjects in the efficacy-evaluable population succeeding on the endpoint. Refer to the following table for a summary of the primary efficacy data for Study DEX-10-16.

Table 1. Primary Endpoint Results for Study DEX-10-16

Surgical Group	Efficacy Evaluable Population	Composite Endpoint Success	Adequately Sedated 80%	No Rescue Midazolam	No ventilation or hemodynamic intervention
All	78	2 (2.6%)	30 (38.5%)	19 (24.3%)	69 (88.5%)
Non-invasive	41	2 (4.9%)	21 (51.2%)	13 (31.8%)	38 (92.7%)
Minimally invasive	25	0 (0%)	7 (28%)	5 (20%)	19 (76%)
Surgical	12	0 (0%)	2 (16.7%)	1 (8.3%)	12 (100%)

Source: Dr. Leah Crisafi's Primary Clinical Review of NDA 021038 supplement 28, p. 27 (PDF), August 9, 2016.

Dr. Crisafi, the primary clinical reviewer for PAS 28, described two possibilities for the failure of the study. First, a high percentage of subjects in the adult studies required rescue sedation, suggesting that the need for rescue in the pediatric studies would also be high. Therefore, the demonstration of statistical significance on a primary endpoint that required no rescue sedation for success seems unlikely. And second, Dr. Crisafi concluded that the optimal starting maintenance dose, 0.6 mcg/kg/h, was too low for the procedures evaluated.

Despite the failed study, the Applicant proposed including the results from Study DEX-10-16 in the Precedex labeling, stating that the study "was designed primarily as a safety study to satisfy PREA and not to support a new labeling indication in the pediatric population." Because dexmedetomidine is widely used in pediatric patients, the Division did not agree that the PMR had been fulfilled and stated that recommended pediatric dosing information needs to be included in labeling. The sNDA received a Complete Response (CR) on August 19, 2016, with the following deficiency identified:

> *The proposed modification to Section 8.4 Pediatric Use section of the package insert can be interpreted to reflect that the Study DEX-10-16 demonstrated a lack of efficacy. However, we believe the study was not adequately designed to support a conclusion about the efficacy of Precedex in the population studied and, therefore, the proposed language is unacceptable.*

The Division recommended the Applicant consult with clinical experts regarding the use of Precedex for pediatric procedural sedation to inform the study design, which should reflect the way Precedex is used in clinical practice, and advised the Applicant to consider dosing, concomitant medications including rescue and analgesics, and types of procedures proposed for evaluation. The Division further stated that if the Applicant opted to evaluate less invasive procedures, a detailed rationale would be needed.

In a meeting package received on September 25, 2017, the Applicant included information from the published literature and from clinical experts (i.e., pediatric anesthesiologists) to

support an evaluation of dexmedetomidine in pediatric subjects undergoing a single non-invasive procedure, such as an imaging procedure, to inform pediatric dosing and satisfy PREA requirements. The Applicant stated that dexmedetomidine is not used as a sole agent for sedation during painful or invasive procedures, and requested concurrence from the Division that a study in pediatric subjects undergoing MRI scanning would satisfy the requirements of PREA. The Division stated the proposed study (Study C0801039) "has the potential to fulfill the PMR requirement" (meeting minutes dated May 2, 2018).

In addition to the discussion regarding proposed evaluated procedures, the Division also discussed the acceptability a waiver request for subjects less than one month of age. The Division stated, "given our current knowledge regarding dexmedetomidine use in this patient population, a request for a partial waiver for patients <1 month of age appears appropriate."

On April 30, 2020, the Applicant submitted PAS 39 to provide "an update to Section 8.4 Pediatric Use of the USPI regarding pediatric use of Precedex." Data from a new study (C0801017), as well as data from previously completed studies (DEX-08-01, DEX-08-05, DEX-09-08, DEX-11-01, DEX-11-06, and CHOP), all conducted in Japanese pediatric subjects, were included in PAS 39. The supplemental NDA received a Refuse to File letter (dated June 25, 2020) based on missing clinical summaries, no rationale for the acceptability of foreign data to the U.S. patient population, missing investigator financial disclosures, and incorrect dataset format. The Applicant withdrew PAS 39 on August 25, 2020.

The Applicant submitted PAS 47 on May 18, 2022, which proposed to add a new indication, pediatric procedural sedation, to the Precedex labeling, and to fulfill PMR 1772-1 based on data from Study C0801039. However, it was determined that this submission should have been a CR, Class 2 resubmission to PAS 28, and the Applicant withdrew it on June 16, 2022. A CR, Class 2 resubmission for PAS 28 was received on June 17, 2022. The results from Study C0801039 and the acceptability of the proposed labeled dosing will be the primary focus of this review.

3. Product Quality

No chemistry, manufactures, or control (CMC) information was submitted in support of this sNDA. The formulation of Precedex approved for use in adult patients is the same as that proposed for use in patients one month to less than 18 years of age. The lower recommended dosing for pediatric patients can be administered by adjusting the infusion rate. A separate formulation is not needed for accurate dosing in this population. The Division concurs that no additional CMC information is needed to support the safety of Precedex for pediatric sedation during non-invasive procedures.

A Claim of Categorical Exclusion for Environmental Assessment was submitted based on the lower dose and duration recommended for pediatric patients. The CMC review team deemed it acceptable.

4. Nonclinical Pharmacology/Toxicology

The Applicant has stated that data from their nonclinical development program demonstrate an acceptable safety profile for the use of Precedex in pediatric patients. A review of the information in the published literature suggests there may be potential neuroprotective effects of Precedex with respect to the developing brain when exposed to other neurotoxic anesthetic agents, although definitive conclusions are challenging and any benefit may be dependent on the setting of use. The Applicant has concluded that data from the nonclinical studies in combination with information from the published literature do not adversely impact the benefit:risk profile of Precedex when administered to pediatric patients.

The following information is excerpted from Dr. Newton Woo's Pharmacology/Toxicology NDA Review and Evaluation.

> *The Spsonsor provided a summary of nonclinical data from juvenile animal studies (JAS) that were previously submitted to the NDA. The reader is referred to the nonclinical review by Dr. Woo dated 5/23/2013 that reviews these nonclinical JAS data. Further, the Applicant conducted a literature search and identified two publications Sun et al., 2020 and Perez-Zoghbu et al., 2020.*
>
> *Taken together, the submitted JAS data along with the nonclinical publications to date demonstrate that dexmedetomidine does not produce neuroapoptosis to levels reported with other anesthetics. Recent literature indicates that dexmedetomidine may have potential neuroprotective effects in neonatal animals when exposed to anesthetics but in a recent publication, higher doses of dexmedetomidine may potentiate anesthetic induced neuroapoptosis in the developing brain. The Applicant has concluded that the previously conducted JAS studies and cited articles do not negatively impact the benefit:risk of dexmedetomidine for pediatric use and does not propose any changes to any of the nonclinical sections of the label. After review of the nonclinical summary, this Reviewer agrees that no new relevant nonclinical information for dexmedetomidine was identified for inclusion into the label at this time.*

The Division concurs with Dr. Woo's conclusions, and agrees the nonclinical sections of the label do not need to updated at this time.

5. Clinical Pharmacology

The Applicant did not capture PK data during Study C0801039; however, as noted in Section 2 of this review, pediatric population PK (popPK) data were captured in four previously completed studies to fulfill the PWR issued in 2007. The data from those studies were reviewed during the review cycles for PAS 21 and PAS 22. Because there were concerns regarding the efficacy data, use of rescue, and safety issues, pediatric information was only added to Section 8.4 of the label at that time. In the current PAS (28), the Applicant is relying on PK data from the four previously completed studies, as well as data from Study C0801017.

Study C0801017 was an evaluation in 46 Japanese pediatric patients from 45 weeks corrected gestation to less than 17 years of age receiving dexmedetomidine infusions during surgery and continuing in an ICU. A total of 308 PK observations were captured. The PK data from this study were applied to the final popPK model from the four previously completed studies to evaluate the performance of the established popPK model to predict dexmedetomidine concentrations in pediatric patients. The following summary is reproduced from Dr. Srikanth Nallani's clinical pharmacology review.

> *The applicant's submitted population PK (popPK) results can be reproduced during the review. In summary, PopPK model from the global studies is appropriate to describe DEX PK in Japanese pediatric participants. Estimated individual PK parameters in Japanese pediatric patients using the final population PK model from the global studies were within the range of those in non-Japanese pediatric patients, suggesting the PK similarity between these populations.*

The Applicant included PK data from patients less than one month of age in Section 12 of the draft label. Because the proposed indication will include patients one month of age and older, the clinical pharmacology review team recommends deletion of the PK information for children less than one month of age, but otherwise has no concerns with the information included in the label. The Division concurs with the team's recommendation.

6. Clinical Microbiology

Precedex is not an antimicrobial agent; therefore, clinical microbiological data are not needed to support the safety of Precedex for pediatric sedation during non-invasive procedures.

7. Clinical/Statistical- Efficacy

The data from Study C0801039 are the basis of support for the proposed non-invasive procedural sedation indication in pediatric patients one month to less than 18 years of age. The focus of the discussion in this section is on the high-dose DEX group efficacy results, given that is the dosing regimen proposed for inclusion in the Precedex prescribing information.

Study C0801039 was a Phase 3/4 randomized, double-blind, dose-ranging study of the efficacy (and safety) of Precedex (DEX) when used with propofol as needed for sedation during MRI scanning. The study was conducted between February 18, 2020, through November 2, 2021, at seven sites in Japan and 14 sites in the U.S. The Applicant cited the primary objective of the study was to assess the efficacy of DEX for pediatric procedural sedation as measured by the percent of subjects at the high dose level versus the low dose level in the combined age cohorts who did not require concomitant propofol to achieve adequate sedation. The only procedure evaluated in the study was MRI.

Study Design

The primary efficacy endpoint was the percent of subjects at the DEX high dose level versus the low dose level in the combined age cohorts who did not require concomitant propofol to

complete the MRI. Subjects in two age groups were randomized 1:1:1 to one of three dosing groups as described in the following tables.

Table 2. Blinded Dose Levels for Subjects One Month to Less than Two Years of Age

Dose Level	DEX Loading Dose	DEX Maintenance Infusion Dose
Low dose level	0.5 mcg/kg	0.5 mcg/kg/hour
Middle dose level	1 mcg/kg	1 mcg/kg/hour
High dose level	1.5 mcg/kg	1.5 mcg/kg/hour

Source: Study C0801039 Report Body, p. 27 (PDF), Applicant's submission, NDA 021038.

Table 3. Blinded Dose Levels for Subjects Two to Less than 17 Years of Age

Dose Level	DEX Loading Dose	DEX Maintenance Infusion Dose
Low dose level	0.5 mcg/kg	0.5 mcg/kg/hour
Middle dose level	1.2 mcg/kg	1 mcg/kg/hour
High dose level	2 mcg/kg	1.5 mcg/kg/hour

Source: Study C0801039 Report Body, p. 27 (PDF), Applicant's submission, NDA 021038.

Dosing in the low dose level was similar in the two age groups, with subjects in the older cohort receiving a higher middle and high loading dose. Depth of sedation was assessed using the Pediatric Sedation State Scale (PSSS), and target sedation for this study was a score of two, defined as quiet (asleep or awake), not moving during procedure, and no frown or verbalization of any complaint. If adequate sedation was not achieved within five minutes following administration of the loading dose and initiation of the maintenance infusion, propofol rescue sedation could have been administered per clinical judgement. While propofol is not indicated for procedural sedation or monitored anesthesia care in the pediatric population, the bolus and infusion doses administered were reasonable and consistent with current clinical practice; i.e., bolus of 0.5 mg/kg following by infusion beginning at 50 mcg/kg/min titrated in 25 to 50 mcg/kg/min increments as needed.

Per the Statistical Analysis Plan (SAP), 40 subjects were planned for enrollment per each dosing group, and 20 subjects were planned for enrollment for each age cohort. The Division recommended at least 18 subjects be enrolled in any dose group and age cohort. Total enrollment was estimated to be 120 subjects. The sample size was calculated to provide 99% power for a 2-sided test with alpha=0.05 for the primary endpoint, assuming the percentage of subjects not requiring rescue propofol was 15% in the low dose group and 60% in the high dose group, with an assumed failure rate of 5%. The following table summarizes the number of treated subjects by country per dose group and age cohort.

Table 4. Subject Exposure, Study C0801039

Dose Groups	Age 1 month to <2 years, n	Age 2 to <17 years, n
Low Dose		
U.S.	18	13
Japan	2	9
Total	20	22
Middle Dose		
U.S.	13	13
Japan	8	8
Total	21	21
High Dose		
U.S.	14	17
Japan	4	3
Total	18	20

*Low, middle, and high maintenance infusion dosing was the same for both age groups; only the loading dose varied.
Source: Reviewer's table.

High dose DEX subject exposure for the combined age cohorts was a total of 38 subjects, 7 Japanese and 31 U.S. subjects.

Key Eligibility Criteria

Inclusion Criteria:

- Male or female (non-childbearing potential) one month to less than 17 years of age
- American Society of Anesthesiologists Physical Status (ASA-PS) classification I, II, or III
- Requires non-intubated, spontaneous breathing, moderate to deep sedation for an MRI lasting at least 20 minutes but no more than three hours

Exclusion Criteria:

- Acute or chronic medical or psychiatric condition
- Pregnant or breastfeeding female subjects
- Fertile male subjects and female subjects of childbearing potential who are sexually active and unwilling or unable to use contraception for at least 28 days
- Weighing less than the 10^{th} percentile or greater than 95^{th} percentile of weight for age and sex
- Craniofacial abnormality
- Requires endotracheal intubation or laryngeal mask airway
- Neurological or psychiatric condition that could confound depth of sedation assessment
- Received treatment with an α-2 agonist or antagonist within 14 days prior to study drug treatment
- Received any pre-induction medication within in four hours prior to study drug treatment

- Known second- or third-degree heart block or clinically significant abnormal ECG findings
- Symptomatic cardiac or respiratory disease
- Requirement for an apnea monitor within the past three months, or moderate to severe Sleep Apnea Syndrome
- SpO_2 less than 93% on room air (increased from 90% in protocol amendment 2)
- Acute febrile illness
- Bradycardia immediately prior to study drug administration
- Hypotension immediately prior to study drug administration

Study Results

As summarized in the following table, there was a statistically significant difference observed for subjects in the high-dose DEX group compared to the low-dose DEX group who did not require propofol rescue for successful completion of the MRI. Note that the primary endpoint was evaluated for the combined age cohorts.

Table 5. Percentage of Subjects who did not Require Propofol Rescue to Complete the MRI, High Dose versus Low Dose (Full Analysis Set)

		High Dose n (%) 95% CI*	Low Dose n (%)95% CI*	Odds ratio 95% CI**	p-value**
Total	N=122	24/38(63.2%)(0.46,0.78)	6/42(14.3%)(0.05,0.29)	0.10(0.03,0.29)	<0.001

Participants that did not require Propofol for sedation based upon achieving target sedation.
Odds ratio was assessed for the difference between treatment groups in percentage of Participants that did not require Propofol for sedation
* Exact 95% CI of proportion of not requiring PRO in each dose level.
**p-values are from PROC FREQ CMH statistics.CI is confidence interval of odds ratio.
PFIZER CONFIDENTIAL SDTM Creation: 21DEC2021 (06:07) Source Data: adpr Table Generation: 07FEB2022 (07:26)
(Database snapshot date : 17DEC2021) Output File: ./cdisc_csr/C0801039/adcm_s011
Table 14.2.1.1 Dexmedetomidine is for Pfizer internal use.

Source: Study C0801039 Report Body, p. 46 (PDF), Applicant's submission, NDA 021038.

Results from the key secondary efficacy endpoint, percent of subjects in the high dose DEX group who do not require concomitant propofol in each age cohort, are summarized in the following table, and demonstrate that the high-dose DEX group maintained statistically significant differences over the low-dose DEX group when each age cohort was evaluated individually.

Table 6. Percentage of Subjects who did not Require Propofol Rescue to Complete the MRI by Age Cohort, High Dose versus Low Dose (Full Analysis Set)

		High Dose n (%) 95% CI*	Low Dose n (%)95% CI*	Odds ratio 95% CI**	p-value**
>=1mn-<2yr	N=59	9/18 (50.0%) (0.26,0.74)	3/20 (15.0%) (0.03,0.38)	0.18(0.04,0.82)	0.022
>=2yr-<17yr	N=63	15/20 (75.0%) (0.51,0.91)	3/22 (13.6%) (0.03,0.35)	0.05(0.01,0.26)	<0.001

Participants that did not require Propofol for sedation within age group based upon achieving target sedation.
Odds ratio was assessed the difference between treatment groups in Percent of Participants that did not require Propofol for sedation.
* Exact 95% CI of proportion of not requiring PRO in each dose level.
**p-values are from PROC FREQ CMH statistics.CI is confidence interval of odds ratio.
PFIZER CONFIDENTIAL SDTM Creation: 21DEC2021 (06:08) Source Data: adpr Table Generation: 07FEB2022 (07:29)
(Database snapshot date : 17DEC2021) Output File: ./cdisc_csr/C0801039/adcm_s0221
Table 14.2.1.2 Dexmedetomidine is for Pfizer internal use.

Source: Study C0801039 Report Body, p. 47 (PDF), Applicant's submission, NDA 021038.

While the results from the key secondary endpoint analysis support those of the primary endpoint analysis, the results from the younger cohort analyses are less impressive, and there was not a statistically significant difference between the high-dose and low-dose DEX groups for the younger Japanese cohort, which consisted of four subjects (p-value 0.264). Treatment failures in both age cohorts required similar doses of rescue sedation for successful completion of the MRI. Specifically, there were no significant differences in the weight- and age-adjusted amount of propofol rescue administered in the two age cohorts in the high-dose DEX group. These data suggest that while the dexmedetomidine dose in the younger cohort resulted in a higher number of treatment failures, those subjects did not require a higher dose of propofol for successful completion of the MRI.

Secondary endpoint analyses evaluating percentage of subjects not requiring propofol to complete the MRI in the high-dose versus middle-dose DEX groups, and in the middle-dose versus low-dose DEX groups also demonstrated statistically significant differences (p=0.015 and p=0.024, respectively). These data support the Applicant's conclusion that higher doses of dexmedetomidine provide adequate sedation for successful completion of MRI in pediatric patients.

The Applicant also evaluated percentage of time at target sedation using the PSSS between the dosing groups. The data from this analysis suggested that percentage of time at target sedation was statistically significantly different in high-dose versus low-dose DEX groups, high-dose versus middle-dose DEX groups, and middle-dose versus low-dose DEX groups depending on the age cohort evaluated. While supportive of the efficacy of higher doses of dexmedetomidine, these analyses were performed on all subjects treated, including those who required propofol rescue, suggesting definitive conclusions regarding the time at target sedation cannot be made.

There were no statistically significant differences in emergence time, defined as time from completion of MRI to a Modified Aldrete Score of nine or greater, between any dose groups for either the combined age cohort or individual age cohorts. However, the median emergence time increased with increasing dexmedetomidine doses. Specifically, the median emergence times per DEX dose group in the combined age cohorts are as follows:

- Low-dose DEX group: 35 min
- Middle-dose DEX group: 42.5 min
- High-dose DEX group: 45.5 min

The same trend in median emergence times was generally observed for each age cohort as well. Based on clinical experience with dexmedetomidine infusions, these results are not unexpected, and in general, longer infusions will delay emergence compared to relatively short infusions. Regarding propofol rescue sedation across the DEX dose groups, the middle-DEX dose group received the highest mean propofol rescue dose (43.1 mg) and the high-dose DEX group received the lowest mean propofol rescue dose (25.8 mg).

Based on the totality of the data reviewed in this sNDA, the Division concludes that substantial evidence of efficacy for high dose dexmedetomidine when used as a sole sedative agent in pediatric subjects during MRI has been demonstrated. The Division further concludes that based on the conditions required for successful MRI scanning in the pediatric population, including required duration of sedation, required depth of sedation, minimal stimulation, spontaneous ventilation without an airway device, and lack of additional sedative or anesthetic agents required, the data from Study C0801039 can be extrapolated to procedures in which the same conditions are needed for successful completion. Therefore, rather than limiting the indication to MRI only, the Division agrees with the Applicant's proposed indication of sedation during non-invasive procedures.

8. Safety

The Applicant is relying on information from Study C0801039 and Study DEX-10-16 to inform the safety profile of Precedex when used for sedation of pediatric subjects one month to less than 17 years of age during MRI; however, only safety data from Study C0801039 are included in the draft labeling.

Regarding review of the safety data from pediatric ICU patients submitted in PAS 21 and PAS 22 to fulfill the PWR, Dr. Crisafi concluded, in her review dated May 23, 2013, that an adequate safety assessment was not possible due to the lack of objectivity and consistency in adverse event reporting, and an overall lack of detail necessary for understanding and verifying severity of recorded hemodynamic adverse events. Additionally, she noted that a possible safety signal for hypotension was observed.

The data from Study DEX-10-16, previously reviewed in 2015, were not adequate to support approval of a pediatric procedural sedation indication for Precedex. Dr. Crisafi noted in her clinical review, dated August 9, 2016, that the doses evaluated in this study were likely too low, which resulted in a high failure rate and the need for rescue sedation. She further concluded that while differences were noted in the incidence of certain adverse events between

the adult studies and Study DEX-10-16, they were not clinically significant, and she recommended they not be described in labeling. She also noted that because the primary efficacy endpoint was not met in this study, the safety profile described may mislead prescribers who use doses that are more effective than those evaluated during this study. Therefore, the data from this study are not discussed further in this review. Refer to Dr. Crisafi's review for additional information regarding the safety information reported in Study DEX-10-16.

The safety issues of greatest concern associated with administration of dexmedetomidine for sedation during noninvasive procedures in spontaneously breathing pediatric patients include changes in measured hemodynamic parameters (i.e., hypotension, hypertension), cardiac arrhythmias (e.g., bradycardia, sinus arrest), changes in respiratory parameters (i.e., bradypnea, apnea), hypoxia, and arousability, some of which are included in Section 5, Warnings and Precautions, of the prescribing information for Precedex based on adult data.

Study C0801039 evaluated 122 pediatric subjects across 21 clinical sites (14 U.S., 7 Japanese) receiving sedation during MRI at three different dose levels. In the one month to less than two years of age cohort, the median total dose was 8.3 mcg, 18.9 mcg, and 22.75 mcg for the low, middle, and high dose DEX groups, respectively. The median duration of treatment ranged from 52.5 to 69 minutes across all three dose groups. In the two to less than 17 years of age cohort, the median total dose was 21.3 mcg, 43.9 mcg, and 80.25 mcg for the low-, middle-, and high-dose DEX groups, respectively. The median duration of treatment was similar to the younger cohort and ranged from 56.5 to 66 minutes across all three dose groups. For both age cohorts, the loading dose was administered over 10 minutes and duration of the maintenance infusion was similar in both age cohorts.

As noted in the eligibility criteria described in Section 7 of this review, subjects with known second- or third-degree heart block, clinically significant abnormal ECG findings, and bradycardia or hypotension immediately prior to the planned start of study drug administration were excluded from participation in this study. Subjects with a history of moderate to severe Sleep Apnea Syndrome, use of an apnea monitor within the previous three months, or oxygen saturation of less than 93% were also excluded.

Deaths, Serious Adverse Events (SAEs), Treatment Discontinuations

There were no subject deaths reported in this study.

There were three subjects who experienced five SAEs.

- Subject C0801039-1013-1002 was a seven-year-old female in the low dose DEX group with a past medical history of abdominal pain and distension, and constipation who experienced acute respiratory failure and severe sepsis on Day 24 following laparoscopic colectomy. Because these SAEs were reported on Day 24, several days after receiving dexmedetomidine for MRI sedation, they are unlikely related to study drug administration.
- Subject C0801039-1037-1001 was a five-year-old female in the low dose DEX group with a past medical history of developmental delay and a seizure disorder who

experienced two seizures (counted as two SAEs) on Days 2 and 21. Given the history of seizures in this subject, study drug administration appears an unlikely causal factor.
- Subject C0801039-1037-1004 was a seven-year-old male in the high dose DEX group with a past medical history of Addison's Disease and adrenoleukodystrophy status post stem cell transplant who experienced hypertension during the maintenance infusion, which resulted in discontinuation of study drug administration.

There were three subjects, one per DEX dose group, in whom study drug administration was discontinued due to an adverse event.
- Subject C0801039-1037-1007 was an 18-month-old male in the low dose group who experienced mild bradypnea during the maintenance infusion (and two minutes after propofol rescue was administered), which led to discontinuation of study drug administration. The propofol rescue likely contributed to the bradypnea given the timing following the first bolus and because additional episodes of bradypnea occurred during the MRI following DEX discontinuation.
- Subject C0801039-1035-1003 was a five-year-old female in the middle dose group, who experienced mild bradycardia following a medication error in the loading dose (received nearly six times intended dose) which led to discontinuation of study drug administration.
- Subject C0801039-1037-1004 was a seven-year-old male in the high dose group (also described above as experiencing an SAE) who experienced hypertension which led to discontinuation of study drug administration.

All adverse events resolved following study drug discontinuation. Of note, dose adjustments were not permitted in this study; therefore, there were no dose reductions or temporary pauses in study drug administration due to AEs.

Cardiovascular- and Respiratory-Related Adverse Events

Adverse events related to changes in measured vital sign parameters were defined using age-based criteria, as described in the clinical protocol reviews by Dr. Crisafi, dated September 18, 2018, and Dr. Alla Bazini, dated June 19, 2019 (IND 032934). Bradycardia was defined as a decrease in heart rate of 30% or more from baseline, or an absolute heart based on the first percentile for age (per Fleming *et al*., 2011)[1], as described in the table below. Of note, the Fleming *et al.* (2011) reference was used in this study to inform vital sign-related adverse events based on the recommendation of Dr. Crisafi during her original review of the study protocol.

[1] Fleming S, Thompson M, Stevens R, *et al*. Normal ranges of HR and RR in children from birth to 18 years of age: a systematic review of observational studies. *Lancet*. 2011;377:1011-1018.

Table 7. Bradycardia Criteria for Adverse Event

Study Criteria for AE of Bradycardia*	
Age	**HR**
≥1 month to <3 months	<107 bpm
≥3 months to <6 months	<104 bpm
≥6 months to <9 months	<98 bpm
≥9 months to <12 months	<93 bpm
≥12 months to <18 months	<88 bpm
≥18 months to <24 months	<82 bpm
≥2 years to <3 years	<76 bpm
≥3 years to <4 years	<70 bpm
≥4 years to <6 years	<65 bpm
≥6 years to <8 years	<59 bpm
≥8 years to <12 years	<52 bpm
≥12 years to <15 years	<47 bpm
≥15 years to <18 years	<43 bpm

*Based on 1st centile data from the HR table in Appendix 7, HR and RR Centile Chart Cut-offs for Children from Birth to 18 Years of Age (Fleming et al, Lancet 2011).

Source: Study C0801039 Final Protocol Amendment 2, p. 86 (PDF), Applicant's submission, IND 032934.

Criteria to assess hypotension as an AE included a decrease in systolic blood pressure (SBP) of 30% or greater. A decrease in SBP of 50% or greater was assessed as a severe AE. Hypotension unresponsive to standard treatment was reported as an SAE. SBP values should have been sustained for at least two consecutive measurements at least five minutes apart.

Criteria to assess hypertension as an AE, based on National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, the Pediatric Vital Signs Reference Chart (pediatric advanced life support [PALS] normal blood pressure by age guidelines), and the advice of clinical expert consultants, are as follows:

- For subjects ages ≥1 month to <1 year: Hypertension was defined as supine SBP≥104 mm Hg and/or DBP ≥56 mm Hg measurements on two or more consecutive occasions taken at least 5 (±1) minutes apart and/or requires intervention.
- For subjects ages ≥1 year to <17 years: Hypertension was defined as supine SBP and/or DBP measurements that are ≥95th percentile for gender, age, and height (stature) on two or more consecutive occasions taken at least 5 (±1) minutes apart and/or requires intervention. Hypertension unresponsive to standard treatment was reported as an SAE.

Adverse events of bradypnea (defined per Fleming *et al.,* 2011), hypoxia, and apnea were based on the criteria summarized in the following tables.

Table 8. Thresholds for Respiratory Rate Adverse Events

Age	Respiratory Rate* (breaths per minute)	Adverse Event Term**
≥1 month to <3 months	<25	Bradypnea
≥3 months to <6 months	<24	
≥6 months to <9 months	<23	
≥9 months to <12 months	<22	
≥12 months to <18 months	<21	
≥18 months to <24 months	<19	
≥2 years to <3 years	<18	
≥3 years to <4 years	<17	
≥4 years to <6 years	<17	
≥6 years to <8 years	<16	
≥8 years to <12 years	<14	
≥12 years to <15 years	<12	
≥15 years to <17 years	<11	

*Rate must be sustained for at least 2 consecutive measurements that are separated by at least one minute and/or requires intervention in order to meet the criteria for AE. If available RR values between the scheduled readings meet the criteria for bradypnea, the AE should be reported. Based on the 1st centile data from the RR table in Appendix 7, HR and RR Centile Chart Cut-offs for Children from Birth to 18 Years of Age (Fleming et al, Lancet 2011).
**This term should be used unless the decreased respiratory rate is part of a larger constellation of signs and symptoms documented as another adverse event.

Source: Study C0801039 Final Protocol Amendment 2, p. 88-89 (PDF), Applicant's submission, IND 032934.

Table 9. Thresholds for End-tidal Carbon Dioxide and Oxygen Saturation Adverse Events

	Value	Adverse Event Term*
SpO_2	<90% for any duration	Hypoxia
Capnography	$EtCO_2 = 0$ for ≥30 seconds	Apnea

*These terms should be used unless the $EtCO_2$ and/or SpO_2 finding(s) are part of a larger constellation of signs and symptoms documented as another adverse event. In determining whether an apnea or hypoxia AE has occurred the clinician should verify the nasal capnograph or SpO2 monitor is in the right location and functioning properly.

Source: Study C0801039 Final Protocol Amendment 2, p. 88-89 (PDF), Applicant's submission, IND 032934.

The most frequently reported treatment emergent adverse events (TEAEs)[2] and treatment-related TEAEs, incidence ≥5%, for all dose groups included bradypnea, bradycardia, hypertension, hypotension, hypoxia, diastolic hypertension, systolic hypertension, and tachycardia. In both the combined and individual age cohorts, the following changes in the incidence of some of these adverse events were observed with increasing DEX dose (findings summarized in Table 10).

- Decreased incidence of bradypnea, hypoxia, and hypotension
- Increased incidence of bradycardia and hypertension

[2] Defined as those AEs beginning on or after the start of study drug administration on Day 1 through Day 2 (the end of the DEX infusion plus 26 hours).

Table 10. Summary of Cardiovascular- and Respiratory-Related TEAEs (Both Age Cohorts, Safety Population)

Number of Participants Evaluable for AEs Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	Low Dose (N=42) n (%)	Middle Dose (N=42) n (%)	High Dose (N=38) n (%)	Total (N=122) n (%)
With Any adverse event	34 (81.0)	27 (64.3)	22 (57.9)	83 (68.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	34 (81.0)	27 (64.3)	22 (57.9)	83 (68.0)
Bradypnoea	33 (78.6)	27 (64.3)	22 (57.9)	82 (67.2)
Hypoxia	6 (14.3)	3 (7.1)	1 (2.6)	10 (8.2)
Tachypnoea	1 (2.4)	0	0	1 (0.8)

Participants are only counted once per treatment per event.
Totals for the No. of Participants at a higher level are not necessarily the sum of those at the lower levels since a participant may report two or more different adverse events within the higher level category.
Includes all data collected since the first dose of study drug.

Number of Participants Evaluable for AEs Number (%) of Participants: by SYSTEM ORGAN CLASS and Preferred Term	Low Dose (N=42) n (%)	Middle Dose (N=42) n (%)	High Dose (N=38) n (%)	Total (N=122) n (%)
With Any adverse event	34 (81.0)	34 (81.0)	36 (94.7)	104 (85.2)
CARDIAC DISORDERS	26 (61.9)	24 (57.1)	27 (71.1)	77 (63.1)
Bradycardia	24 (57.1)	24 (57.1)	27 (71.1)	75 (61.5)
Rebound tachycardia	0	0	1 (2.6)	1 (0.8)
Sinus arrhythmia	0	0	1 (2.6)	1 (0.8)
Tachycardia	3 (7.1)	1 (2.4)	1 (2.6)	5 (4.1)
VASCULAR DISORDERS	23 (54.8)	26 (61.9)	27 (71.1)	76 (62.3)
Diastolic hypertension	3 (7.1)	3 (7.1)	4 (10.5)	10 (8.2)
Diastolic hypotension	1 (2.4)	1 (2.4)	0	2 (1.6)
Hypertension	11 (26.2)	17 (40.5)	18 (47.4)	46 (37.7)
Hypotension	13 (31.0)	11 (26.2)	6 (15.8)	30 (24.6)
Systolic hypertension	1 (2.4)	5 (11.9)	3 (7.9)	9 (7.4)
Withdrawal hypertension	0	0	1 (2.6)	1 (0.8)

Source: ISS, pp. 28-29 (PDF), Applicant's submission, NDA 021038

A possible explanation for the decreased incidence of bradypnea, hypoxia, and hypotension observed with increasing DEX dose is the increased use of propofol rescue in the low- and middle-dose DEX groups. Propofol has clinically significant effects on measured respiratory and hemodynamic parameters, including these three changes. Regarding the incidence of hypertension observed with increasing doses of DEX, the majority of cases (i.e., 12) reported hypertension beginning during the loading dose and continuing through at least a portion of the maintenance infusion, suggesting the higher loading dose (compared to the low- and middle-dose groups) may have contributed to the increased incidence. Also, transient

hypertension, which was observed in adult DEX studies primarily during the loading dose, is already described in the DEX prescribing information.

No patterns were observed for diastolic hypertension (highest incidence reported in high dose group), systolic hypertension (highest incidence reported in middle dose group), and tachycardia (highest incidence reported in low dose group).

Cardiovascular- and Respiratory-Related Adverse Events Occurring with an Increased Incidence in Pediatric versus Adult Subjects

The adverse events that were reported with an increased incidence in pediatric subjects in the high dose DEX group in Study C0801039 compared to adult subjects undergoing procedural sedation in Studies 2005-005 (elective surgery requiring monitored anesthesia care) and 2005-006 (awake fiberoptic intubation) include bradycardia (71% pediatric subjects vs. 14% adult subjects), bradypnea/respiratory depression (58% pediatric subjects vs. 37% adult subjects[3]), hypertension (47% pediatric subjects vs. 13% adult subjects), and hypoxia (3% pediatric subject vs. 2% adult subjects). While the differences in incidence in bradycardia, bradypnea, and hypertension between pediatric and adult subjects were large, and appear higher than some rates reported in the published literature, they do not adversely impact the safety profile of dexmedetomidine use in pediatric patients for sedation for six main reasons.

First, as noted above, the criteria used to determine a vital sign-related adverse event in Study C0801039 were based on the age-based cut-off values described in Fleming *et al.,* (2011). These criteria define vital sign-related adverse events, specifically bradycardia and bradypnea, that appear to be more conservative than that used in other pediatric sedation studies and in the adult studies conducted to add a procedural sedation indication to the Precedex label. For example, some texts[4] use a heart rate cut-off of 100 beats per minute (bpm) to define bradycardia in the birth to less than three-month-old population, while Fleming *et al.* uses 107 bpm to define bradycardia.

Second, in the adult studies, and in published pediatric procedural sedation studies, the dexmedetomidine dosing regimen differed than that used in Study C0801039. Specifically, in the adult studies, the infusion of dexmedetomidine could be titrated based on clinical effect or the occurrence of adverse events. In Study C0801039, there were no dose-adjustments permitted, aside from treatment discontinuation. This suggests that the adult studies may have reported fewer vital sign-related adverse events if the dose was adjusted to prevent the occurrence of an adverse event.

Third, all adult subjects in Study 2005-006 received glycopyrrolate 0.1 mg i.v. prior to administration of the study drug. This pretreatment clearly would have impacted the number and severity of reported bradycardic events.

[3] In response to an IR, the Applicant clarified that bradypnea in adults was not a prespecified adverse event, and that it was recorded as an AE based on individual investigator assessment. Therefore, for comparison purposes, the AE of respiratory depression in adults was used.
[4] Nelson Textbook of Pediatrics, 20th Ed., 2016.

Fourth, the adverse event data summarized in Table 7 in the label includes treatment failures (subjects who received propofol rescue), which would have clearly impacted the incidence of reported adverse events. While the impact of propofol administration would likely be greater in the low and middle dose DEX groups given the higher proportion of subjects rescued with propofol in those treatment groups, there were 14 subjects in the high-dose DEX group who failed study drug treatment, and many of them experienced adverse events.

Fifth, the majority of vital sign-related adverse events were mild in severity. Only two subjects in the high dose DEX group required anticholinergic treatment for bradycardia, and no subject in any dose group required airway intervention, including jaw thrust or insertion of a naso- or oropharyngeal airway, for bradypnea (refer to Table 11 for adverse events requiring intervention).

And sixth, given the widespread off-label use of dexmedetomidine the pediatric population, changes in measured hemodynamic parameters, particularly bradycardia, are anticipated, and therefore, generally treated quickly[5,6].

A final consideration is that Study C0801039 was a relatively small study, evaluating a total of 122 subjects, such that the percentage of a specific adverse event would likely appear high.

Adverse Events Requiring Intervention

The following table summarizes the adverse events reported in seven subjects that resulted in a clinical intervention.

Table 11. Adverse Events Requiring Intervention by Dose Group

Low Dose Group	Middle Dose Group	High Dose Group
12-year-old female received an i.v. bolus of lactated ringers (LR) solution for hypotension during the maintenance infusion	7-year-old female received an i.v. bolus of LR for diastolic hypotension during the maintenance infusion	8-year-old female received atropine for bradycardia during the maintenance infusion
9-year-old female received supplemental oxygen for hypoxia and bradypnea during the maintenance infusion; 5-year-old female received supplemental oxygen for hypoxia during maintenance infusion	6-month-old subject received supplemental oxygen for bradypnea during the maintenance infusion	7-year-old male* received glycopyrronium for bradycardia during the loading dose and hydralazine for hypertension during the maintenance infusion

*Subject C0801039-1037-1004 discussed above as discontinuing treatment for an AE.

No subject required airway intervention, including jaw thrust or chin lift, naso- or oropharyngeal airway, or airway instrumentation.

[5] Mahmoud, M, *et al.* Dexmedetomidine: What's new for pediatrics? A narrative review. *J of Clin Med.* 2020;9(2724):1-23.
[6] Mahmoud, M. *et al.* Dexmedetomidine: review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations. *Brit J of Anaes.* 2015:171-182.

Moderate Adverse Events
The majority of TEAEs were mild, with the exception of five subjects who experienced TEAEs of moderate severity, summarized in the following table. No subject experienced a severe TEAE.

Table 12. Moderate TEAEs

Low Dose Group	High Dose Group
1-year-old female experienced moderate hypoxia	8-year-old female experienced moderate bradycardia
12-year-old female experienced moderate hypotension+	7-year-old male experienced moderate bradycardia, tachycardia, and hypertension (this subject described above under treatment discontinuations)
2-month-old female experienced moderate hypertension*	

*This subject was not included in the summary of subjects experiencing moderate AEs provided by the Applicant. +This subject also described in Table 11.

Of note, four of the five subjects described in the table above required propofol rescue sedation. The eight-year-old female who experienced moderate bradycardia in the high dose DEX group did not require propofol rescue for successful completion of the MRI. This suggests that propofol may have contributed to the other AEs described, at least in part.

While there were differences in the observed incidences of TEAEs during the loading dose and maintenance infusions, the severity and type of TEAEs were similar.

Withdrawal-Related TEAEs
The Applicant used the Pediatric Anesthesia Emergence Delirium (PAED) scale to assess for delirium in Study C0801039. The PAED is a validated five-item rating scale, where each item is assessed ranging from 'not at all' to 'extremely.' A score of 10 or greater was used to identify subjects in this study with emergence delirium.

There were 11 subjects (approximately 9%) who had a score of 10 or greater on the PAED; five in the high dose group, two in the middle group, and four in the low dose group. The Applicant reported that of these 11 subjects, only two had emergence delirium and one had agitation that were described as withdrawal-related adverse events. The three events are described in both Section 5 and Section 6 of the draft labeling. One subject in the one month to less than two years of age cohort treated with high dose DEX experienced emergence delirium), which resolved within six minutes. One subject in the two to less than 17 years of age cohort treated with middle dose DEX experienced emergence delirium which resolved within 21 minutes. One subject in the two to less than 17 years of age cohort treated with high dose DEX experienced agitation which resolved within 16 minutes.

In response to an IR, the Applicant clarified that not all subjects (i.e., only three of 11) with a PAED score of 10 or greater were reported as experiencing an adverse event of emergence delirium given that clinical judgement is necessary to confirm the diagnosis. Specifically, the Applicant stated that a score of 10 or greater on the PAED triggered a clinical evaluation by a study investigator to determine whether there were other clinical findings that informed the

diagnosis of emergence delirium, and hence recorded as an AE. The Applicant also stated that while there were only three cases of emergence delirium and agitation, inclusion of this withdrawal reaction in Section 5 is important to inform providers of the risk, particularly because many providers are unaware that dexmedetomidine can result in transient withdrawal reactions.

In sum, the Division concludes that the data from Study C0801039 adequately characterize the clinical utility and benefit, and risks associated with administration of dexmedetomidine in pediatric subjects undergoing MRI. While the incidence of some adverse events occurred with a higher frequency than that observed in adults undergoing procedural sedation, the Division concludes that these data do not preclude approval because there were no *new* safety signals identified, the risks of hemodynamic instability associated with dexmedetomidine administration in adult and pediatric patients are well-known and documented in the published literature, and information in the label informs providers of these risks, and describes acceptable patient populations and mitigation strategies. Therefore, the benefit:risk assessment for a pediatric non-invasive procedural sedation indication (refer to the discussion in Section 7 of this review for the acceptability of extrapolation of the MRI study data to non-invasive pediatric procedures) and the proposed dosing are favorable, and the indication can be approved.

9. Advisory Committee Meeting

There were no specific issues that needed be discussed with an advisory committee (AC); therefore, an AC meeting was not convened.

10. Pediatrics

The information submitted in this pediatric efficacy sNDA fulfills the outstanding PREA PMR. Additional evaluations in pediatric subjects less than one month of age or during other diagnostic or therapeutic procedures are not required for two reasons. First, the Division agrees with the Applicant's request for a waiver for an evaluation in the less than one month age group, based on the commonly used feed-and-swaddle non-sedate method. And second, dexmedetomidine does not generally provide adequate sedation for any invasive diagnostic or therapeutic procedure or surgery when administered as a sole agent. This sNDA was discussed with PeRC, and the members agreed that the data from this study satisfy the outstanding PREA PMR.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI)
Two clinical sites, Site 1005 (Umar Khan; Dallas, TX) and Site 1015 (Cassandra Duncan-Azadi; Oklahoma City, OK), were selected for inspection for the following reasons:

- Both sites are in the U.S. While Japanese sites did enroll subjects in this study, the majority of subjects were enrolled in U.S. sites (i.e., 72%).

- Good site efficacy
- No previous inspections

Results from the clinical site inspections did not identify any issues or data irregularities that could adversely impact the integrity or interpretation of the reported results. OSI has no outstanding concerns that would prevent approval of this sNDA.

One investigator, Stefanie Schrum from investigative site 1023, was included on FDA Form 3455, DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS, as having owned Pfizer shares totaling $123,052.16. This site treated three subjects. The Division concludes that the financial interest of this single investigator for a site which enrolled a low number of subjects does not adversely impact the interpretability of the study data, and the results are valid.

12. Labeling

- INDICATIONS AND USAGE:
  As noted previously, based on the acceptability of extrapolating data from Study C0801039 to other non-invasive procedures, the Division agreed with the Applicant's proposed indication of sedation of non-intubated pediatric patients aged 1 month to 16 years prior to and during non-invasive procedures, with the exception that the Division will include less than 18-year-old patients in the indication. The Division's current thinking is that the PK, safety, and efficacy data from the pediatric population evaluated in Study C0801039 are also applicable to less than 18-year-old (less than 18-year-old) patients. Specifically, pharmacokinetics/pharmacodynamics, and clinical response to treatment are likely going to be similar between 16-year-old patients and less than 18-year-old patients. Therefore, extrapolation of these data is acceptable and the indication will include this age group.

- DOSAGE AND ADMINISTRATION:
  The Applicant's Recommended Dosage Table described adult and pediatric dosing, using different rows for different indications. DPMH recommended this table be split into two tables to separate the adult and pediatric dosing to improve clarity and readability. Furthermore, the Division recommended the Procedural Sedation dosing for pediatric patients be changed to Sedation of Pediatric Patients During Non-Invasive Procedures.

- WARNINGS AND PRECAUTIONS:
  The Division agreed with the Applicant's edits to this section, specifically Section 5.5 Withdrawal, proposing to include emergence delirium and agitation. While there were a low number of cases of withdrawal reactions reported in Study C0801039, the Division agreed inclusion of this information is important for clinicians.

- ADVERSE REACTIONS:
  Based on the large differences in the incidence of certain vital sign-related adverse reactions, the Division recommended the Applicant include information regarding the

pretreatment of adult subjects with glycopyrrolate in one procedural sedation study, to partially explain the difference in the reported incidences of bradycardia. The Division also recommended the Applicant include a statement that no subject required airway intervention, including a jaw thrust or insertion of a nasal or oral airway.

DPMH also recommended that the pharmacokinetic information for subjects less than one month of age be deleted from Table 10 in Section 12 Clinical Pharmacology.

13. Decision/Action/Benefit:Risk Assessment

Regulatory Action
Approval.

Benefit:Risk Assessment
The benefits of Precedex for pediatric sedation during non-invasive procedures for patients one month to less than 18 years of age outweigh the potential risks.

Postmarketing Requirements
There are no outstanding postmarketing requirements or commitments for this application. As noted in Section 10, the PREA PMR has been satisfied with this sNDA.

14. Recommended Comments to the Applicant

None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LISA M BANTA
12/16/2022 04:25:22 PM

RENEE L PETIT-SCOTT
12/16/2022 04:27:56 PM

ALLA T BAZINI
12/16/2022 04:31:20 PM

RIGOBERTO A ROCA
12/16/2022 04:34:50 PM