DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 32,934
NDA 21-038

WRITTEN REQUEST

Hospira, Inc.
275 North Field Drive
Dept. 0389, Bldg. H2-2
Lake Forest, IL 60045

Attention: Tracy Lynch
Director, Regulatory Affairs

Dear Ms. Lynch:

Reference is made to your October 31, 2006, Proposed Pediatric Study Request submitted to IND 32,934 for dexmedetomidine HCl.

To obtain needed pediatric information on Precedex® (dexmedetomidine HCl Injection), the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

I. PHARMACOKINETIC STUDIES

Type of studies:

These studies will be of open-label, dose-escalation design to obtain pharmacokinetic, pharmacodynamic (PD), safety, and efficacy information in order to identify PK variation among different age groups for comparison with the adult PK profile, and to identify the appropriate dosage to be used for different age groups in the subsequent studies. Information will be collected to evaluate the pharmacokinetics of a loading dose infusion and maintenance dose infusion of dexmedetomidine studied by age cohort beginning with pediatric patients who are at the least risk as defined by the inclusion and exclusion criteria. In order to obtain adequate data for PK/PD analyses, a minimum of three escalating loading doses will be evaluated for each age group. Patients who appear to respond favorably from administration of the loading dose will continue to receive dexmedetomidine by a continuous infusion. The rationale for the choice of doses will be provided in the submitted protocols. This rationale may be informed by literature, or current medical practice, and/or dosing in adults.

Objective of studies:

- Characterize the pharmacokinetic profile of dexmedetomidine infusion following a loading dose and maintenance infusion in different pediatric age groups.

- Obtain adequate pediatric PK data to allow for comparison with adult PK data.

- Identify appropriate dosage(s) to be used for different age groups in the subsequent studies, based on comparative exposures related to those in adults or pharmacokinetic/pharmacodynamic analyses.

Number of Patients and Age Groups in which studies must be performed:

Studies must include an adequate number of patients to characterize the key pharmacokinetic parameters of dexmedetomidine and to inform the selection of a therapeutic dose for the age ranges studied, taking into account inter-subject variability. The number of patients must be approximately evenly distributed between genders and must be approximately evenly distributed across the age ranges studied. The following are the minimum number of patients required by age group and must be distributed approximately equally among the doses evaluated. These groups have been determined by assessment of differences in developmental physiology.

- $\geq$ 28 weeks gestational age to <1 month chronological age N= 12
- 1 to < 6 months N= 12
- 6 to < 12 months N= 12
- 12 to < 24 months N= 12
- 2 to < 6 years N= 18
- 6 to $\leq$ 16 years N= 30

A sufficient number of blood samples should be drawn during and after the loading infusion and maintenance infusion to capture the dexmedetomidine PK profile. The total volume of blood drawn and the PK methods to be employed in the data analysis should be determined *a priori* and stated in the protocol. If sparse sampling methods, i.e., population pharmacokinetics, are employed, blood samples should be dispersed throughout the loading infusion, maintenance infusion, and end of infusion periods to ensure proper parameter estimation.

Inclusion criteria:

- Initially intubated and mechanically ventilated pediatric subjects in an intensive care setting

Exclusion criteria:

- Pediatric patients with neurological conditions that prohibit an evaluation of sedation, such as diminished consciousness from increased intracranial pressure or extensive brain injury. Patients with immobility from neuromuscular disease or neuromuscular blocking agents will be excluded from these studies.

- Patients in whom the risk of dexmedetomidine treatment is expected to exceed its benefits, such as patients with second- or third-degree heart block or protocol-defined significant hepatic impairment.

Study Endpoints:

1. Pharmacokinetics:

Descriptive statistics must be reported employing traditional or population PK methods for PK parameters of dexmedetomidine, such as T_{max}, $t_{1/2}$, C_{max}, AUC_{0-t}, AUC_{0-inf}, K_e (elimination rate constant), V_d (volume of distribution), and CL (clearance).

Pharmacodynamic and safety measures described below must be measured at the same time points as PK sampling, to the extent possible, to provide an understanding of the concentration-response relationship. Exposure (infusion rate/dose/AUC/Cmax) must be explored with regard to:

- pharmacodynamic endpoints, such as sedation, time to use of rescue medication, amount of rescue sedation

- safety endpoints, such as heart rate, systolic and diastolic blood pressure and most frequent adverse events

2. Pharmacodynamics:

Age-appropriate sedation scale(s) must be used. The rationale for the choice of the scale(s) and instruments must be provided in the protocol. The same age-appropriate instruments must be used at each study site. Sedation is to be measured at the same time points as PK sampling to provide an understanding of the concentration-response relationship.

All protocols must describe the ascertainment of any painful interventions that may affect study assessments. Protocols must specify the recording and evaluation of the extent to which comfort measures are employed and the patients' responses to handling or other stimuli. Additionally, all protocols must specify that the instruments chosen to evaluate sedation in pediatric patient population subsets will be uniform among study centers.

3. Safety:

- Vital signs (heart rate, blood presssure, respiratory rate, pulse oximetry and/or noninvasive carbon dioxide monitoring, EKG, central body temperature, body weight, input/output fluid balance)

- Incidence of adverse events. Measurements of vital signs and laboratory values that exceed prespecified age-appropriate boundaries will be reported as adverse events

- Preterm infants will be assessed for the occurrence of comorbidities of prematurity, such as intraventricular hemorrhage, necrotizing enterocolitis, sepsis, and persistent ductus arteriosus

- Use of rescue regimens to support vital signs

- Use of adjunct medications

- Incidence of signs of withdrawal including changes in blood pressure

All protocols must specify individual patient study discontinuation criteria. A Data Safety Monitoring Board with prespecified study stopping rules must be stipulated by study protocols.

II. 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. 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. Approximately 50 percent of the patients enrolled must be expected to require sedation for a minimum of 24 hours and include a representative sample of patients who will need sedation for days or weeks. 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.

Objectives of Studies:

- Characterize the loading and maintenance dosing of dexmedetomidine by age group and overall medical condition of patients.

- Evaluate the safety and efficacy of loading and maintenance infusion for sedation in intubated and mechanically ventilated pediatric patients.

- Explore the exposure-response relationship between any available plasma concentrations of dexmedetomidine and age-appropriate validated clinical measures of sedation and safety.

Number of Patients and Age Groups in which studies must be performed:

These groups have been determined by assessment of differences in developmental physiology.

- 28 weeks gestational age to <1 month chronological age
- 1 to < 6 months
- 6 to < 12 months
- 12 to < 24 months
- 2 to < 6 years
- 6 to $\leq$ 16 years

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. A sufficient number of pediatric patients must complete the studies to adequately characterize common adverse events with the study drug at clinically relevant doses.

Inclusion criteria:

- Initially intubated and mechanically ventilated pediatric subjects in an intensive care setting
- Patients classified as American Society of Anesthesiology (ASA) 1 - 4 for presurgical morbidity

Exclusion criteria:

- Pediatric patients with neurological conditions that prohibit an evaluation of sedation, such as diminished consciousness from increased intracranial pressure or extensive brain injury. Patients with immobility from neuromuscular disease or neuromuscular blocking agents will also be excluded from these studies
- Patients in whom the risk of dexmedetomidine treatment is expected to exceed its benefits such as second- or third-degree heart block or protocol-defined significant hepatic impairment

Study Endpoints:

1. Efficacy:

   Validated, age-appropriate sedation scale(s) must be used. The same scales must be used across all study sites. The rationale for the choice of the scale(s) and instruments must be provided in the protocol.

   The primary efficacy analysis will be the percentage of subjects who do not require rescue midazolam for sedation based on achieving and/or maintaining the protocol-specified sedation range using validated and age-appropriate sedation scale(s) when intubated. Criteria for administration of concomitant drugs that can result in sedation must be prespecified and the time of administration of these drugs relative to sedation assessments must be captured. All evaluations will be based upon assessments by blinded assessors.

   Secondary endpoints must include the absolute time and the percentage of time of dexmedetomidine treatment that the patient is sedated within a prespecified range, the amount of rescue medication required, and the time to extubation. The time to first use of rescue sedation and/or analgesic medication must also be analyzed.

   All protocols must describe the ascertainment of any painful interventions that may affect study assessments. Protocols must specify recording and evaluation of the extent to which comfort measures are employed and the patients' responses to handling or other stimuli. Additionally,

all protocols must specify that the instruments chosen to evaluate sedation in pediatric patient population subsets will be uniform among study centers.

2. Safety:

- Vital signs (heart rate, blood pressure, respiratory rate, pulse oximetry and/or noninvasive carbon dioxide monitoring, EKG, central body temperature, body weight, input/output fluid balance
- Incidence of adverse events. Measurements of vital signs and laboratory values that exceed prespecified, age-appropriate boundaries will be reported as adverse events
- Preterm infants will be assessed for the occurrence of comorbidities of prematurity such as intraventricular hemorrhage, necrotizing enterocolitis, sepsis, and persistent ductus arteriosus
- Use of medications to support vital signs
- Use of adjunct medications
- Incidence of signs of withdrawal including changes in blood pressure

All protocols must specify individual patient study discontinuation criteria. A Data Safety Monitoring Board with prespecified study stopping rules must be stipulated by study protocols.

3. Pharmacokinetics:

If additional PK assessments (traditional or population PK) are made, descriptive statistics should be reported for PK parameters of dexmedetomidine, such as T_{max}, $t_{1/2}$, C_{max}, AUC_{0-t}, AUC_{0-inf}, K_e (elimination rate constant), V_d (volume of distribution), and CL (clearance).

Drug Information*:*

Dosage form: Approved intravenous formulation, 118 mcg of dexmedetomidine HCl (equivalent to 100 mcg dexmedetomidine base) and 9 mg of sodium chloride in 1 mL water. The solution is preservative-free and contains no additives or chemical stabilizers

Route of administration: intravenous infusion

Regimen:

Initial dosing in the pharmacokinetics trials will be selected based on adult dosing requirements, literature, current medical practice, data that the company owns, and/or data to which the company has right of reference. Initial dosing in the efficacy trials will be informed by the PK studies. Subsequent dosing in all trials will be given according to criteria established

in the protocol. The dose characteristics (dose in mcg/kg, duration of bolus period where applicable) must be pre-specified in the protocol and recorded in the CRF.

Drug-specific safety concerns:

Adverse event monitoring must include, at a minimum, the following:

- Respiratory depression
- Bradycardia
- Hypotension
- Signs of withdrawal after discontinuation of dexmedetomidine, such as rebound hypertension
- Clinical and laboratory signs and/or symptoms of adrenal suppression including hypotension and/or electrolyte abnormalities
- Appropriate clinical laboratory assessments

All protocols must specify individual patient study discontinuation criteria. A Data Safety Monitoring Board with pre-specified study stopping rules shall be included in all studies.

Statistical information:

The pharmacokinetic and pharmacodynamics studies are non-powered trials that will provide key dosing information for the efficacy trials, and are not powered for inferential testing. Results of all assessments will be presented descriptively.

Efficacy trials must be powered using information from the pharmacokinetic studies and references. The sample size for the treatment arms will be determined based on the estimates of the effect size for the primary efficacy endpoint to show treatment differences. A detailed statistical analysis plan is required prior to beginning enrollment and should accompany the study protocol submission.

A sufficient number of pediatric patients of both genders should complete the studies to adequately characterize the safety of the study drug at clinically relevant doses. Demographic and safety data should be tabulated and a descriptive analysis of safety data should be provided.

Labeling that may result from the studies

Draft labeling must be submitted with appropriate sections of the label changed to incorporate the findings of the studies.

Format of reports to be submitted:

You must submit full study reports, not previously submitted to the Agency, addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White. For ethnicity, one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/cder/regulatory/ersr/Studydata-v1.1.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/cder/guidance/6766fnl.pdf.

Timeframe for submitting reports of the studies:

Reports of the above studies must be submitted to the Agency on or before March 31, 2012. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request:

As per the Best Pharmaceuticals for Children Act, section 4(a), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request, then you must indicate when the pediatric studies will be initiated.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

If you have any questions, call Allison Meyer, Regulatory Project Manager, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director,
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Meyer

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