DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Attention:

Dear:

To obtain needed pediatric information on this active moiety, 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 studies in pediatric patients described below. These studies investigate the use of intravenous (IV) morphine for analgesia in pediatric patients.

Background:
Morphine sulfate is commonly used for analgesia in pediatric and neonatal intensive care units. However, there is incomplete information available about dosing, pharmacokinetic (PK) parameters, effectiveness, and safety in pediatric patients who receive analgesia with morphine in the intensive care unit setting.

I. SINGLE-DOSE STUDIES

These studies will consist of randomized, adequately controlled, assessor-masked, parallel-arm, fixed-dose superiority (against an acceptable comparator) studies evaluating PK, efficacy, and safety of IV morphine sulfate in opioid non-tolerant[1] pediatric patients with moderate-to-severe pain requiring morphine analgesia. Pharmacokinetic parameters will be assessed in a subset of randomized patients. Rationale for choice of doses must be provided in the submitted protocol. Choice of doses may be guided by the literature or current medical practice. Single-dose data must be evaluated prior to initiating multiple-dose studies.

Objective of Studies:
1. Develop an approach to minimum effective initial dosing of bolus IV morphine in various pediatric age groups.
2. Characterize the PK of single-dose IV morphine.
3. Obtain data to investigate the exposure-response relationship between plasma concentrations of morphine and clinical measures of analgesia.

[1]**The physiologic state in which an increased dosage of an opioid is required to sustain a desired effect.**

Age Groups to be Studied: *These groups have been determined by assessment of differences in developmental physiology and neurocognitive function. A clinical trial in neonatal patients will be separate from a clinical trial in the older pediatric patients.*

Neonatal Patients
- Pre-term infants (stratified by corrected gestational age*)
- Term infants to < 1 month

*Corrected gestational age is defined as the sum of the gestational age plus chronologic age since birth.

Pediatric Patients
- 1 month to < 6 months
- 6 months to < 4 years
- 4 years to < 16 years

Number of Patients:

A sufficient number of patients of both sexes to provide reasonable power (at least 80%) to detect a statistically significant difference in the primary efficacy endpoint will complete the studies. Neonatal and pediatric patients should be approximately evenly distributed between sexes. There should be approximately equal numbers of patients in the age groups and patients should be reasonably distributed within the age ranges. A subset of randomized patients will be identified with sufficient number to characterize PK.

To ensure a sufficient number of pediatric patients will complete the PK studies, a minimum of approximately 6 patients will be needed in each of the following age groups, pre-term infants, term infants to < 1 month, 1 month to < 6 months, 6 months to < 4 years, and approximately 12 evaluable patients 4 years to < 16 years. Sample size estimates for the PK studies are based on traditional PK study design and more patients will be needed if a population PK approach is to be employed. A population PK approach is encouraged, if feasible.

A sufficient number of pediatric patients of both sexes will complete the safety and efficacy studies to adequately characterize the safety of the study drug at clinically relevant doses. This should include a minimum of approximately 10 evaluable patients in each of the following age groups, term infants to < 1 month, 1 month to < 6 months, 6 months to < 4 years, and approximately 20 evaluable patients 4 years to < 16 years.

Entry Criteria:

Opioid non-tolerant pediatric patients of both sexes with moderate-to-severe pain, based on validated, age-appropriate pain scale assessments and requiring treatment with an opioid analgesic.

Pediatric patients receiving neuromuscular paralytic agents and patients with neuromuscular disease, significant renal impairment (protocol defined), or significant hepatic impairment (protocol defined) will be excluded from these studies. Infants of substance-abusing mothers, infants of diabetic mothers, and infants with spina bifida will also be excluded from these studies.

Assessment Parameters:

1. Pharmacokinetic:

A subset of randomized patients in numbers sufficient to characterize the PK parameters of morphine and its primary metabolites, 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 clearance (CL) will be studied. Adequate rationale for excluding any of the aforementioned PK parameters must be provided in the protocol. The subset of patients for PK evaluation should be representative of the larger study population with respect to age and gender. Either a traditional PK or population PK approach may be used.

2. Clinical Efficacy:

It is essential to identify a single primary efficacy outcome reflecting adequacy of analgesia.

- Clinical assessments will be made using validated, age-appropriate instruments. Inter-rater variability will be evaluated. Evaluation will include assessments by masked caretakers and assessors. Rationale for choice of instruments will be provided in the protocol.

Secondary efficacy parameters will include:

- Duration of analgesic effect
- Incidence of inadequate analgesia or oversedation

3. Safety:

- Incidence of adverse events (pre-term infants will also be assessed for comorbidities of prematurity such as intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), chronic lung disease (CLD), necrotizing enterocolitis (NEC), sepsis, and patent ductus arteriosus (PDA).)
- Vital signs (HR, BP, RR, pulse oximetry, EKG. These signs will be collected to capture potential respiratory and hemodynamic consequences associated with analgesia.)
- Rash
- Sedation
- Urine output
- GI intolerance/constipation

All protocols will document any painful interventions that may affect study assessments. The extent to which comfort measures are employed and the patient's response to handling or other stimuli will be recorded and evaluated. All protocols will additionally specify that the instruments chosen to evaluate pain in pediatric patient population subsets will be uniform among study centers.

Statistical Information, Including Power of Study and Statistical Assessments:

These studies must have a pre-specified, detailed statistical analysis plan appropriate to the study design and outcome measures. The studies will be designed to provide at least 80% statistical power to detect a treatment effect, at a conventional level of statistical significance ($p=0.05$). The demographic and safety data will be tabulated and descriptive analysis of safety data will be provided. Descriptive analysis of the PK data must also be provided. A clinically meaningful effect size will be pre-specified and justified in the protocol. It will be discussed with the FDA and agreed upon prior to initiating studies.

II. MULTIPLE-DOSE STUDIES

Type of Studies:

A. **Multiple-Dose Studies:** These studies will consist of multicenter, randomized, assessor-masked, adequately controlled, parallel-arm superiority (against an acceptable comparator) studies evaluating PK, efficacy, and safety of IV morphine sulfate titration in pediatric patients with moderate to severe pain requiring multiple doses of morphine via IV bolus and continuous infusion without initial bolus. Pharmacokinetic parameters will be assessed in a subset of patients. In addition to a control intended to provide assay sensitivity, active control arms to provide comparative information are also encouraged. The studies will evaluate down titration to avoid withdrawal syndrome. Initial dosing will be informed by the results of single-dose studies. Efficacy will be assessed for up to three weeks. Patients will be monitored for signs of withdrawal and other adverse events for at least three days following complete discontinuation of treatment.

B. **Short-Term Safety Studies:** These studies will assess withdrawal in pediatric patients requiring IV morphine sulfate by intermittent IV bolus versus continuous infusion. Study enrollment can include patients from prior studies.

C. **Long-Term Follow-up:** While not part of this written request, prospective studies to investigate the long-term effects of morphine on neurodevelopmental outcomes should be considered. Obtaining data in neonatal and premature infant populations is of particular interest. Patients from studies A and B may be enrolled in this trial.

Objective of Studies:

1. Characterize the metabolism and PK of steady state IV morphine.
2. Obtain data to investigate the exposure response relationship between plasma concentrations of morphine and its primary metabolites, and clinical measures of analgesia.
3. Determine the optimal dosage including the minimum effective dose, interval, and titration schemes for administration of IV morphine when used as a bolus and as a continuous infusion without initial bolus.
4. Investigate efficacy as a function of dose and manner of infusion of IV morphine. Additionally, effects of time on dose (tolerance) may be assessed.
5. Characterize safety in patients randomized to intermittent bolus morphine versus continuous infusion morphine without initial bolus.
6. Evaluate pharmacologic withdrawal associated with discontinuation of morphine following long-term analgesia.
7. Investigate long-term effects of morphine infusion on neurodevelopmental and neurocognitive outcomes in pediatric patients.

Age Groups to be studied: *These groups have been determined by assessment of differences in developmental physiology and neurocognitive function. Clinical trial(s) in neonatal patients will be separate from a clinical trial(s) in the older pediatric patients.*

Neonatal Patients

- Pre-term infants (stratified by corrected gestational age*)
- Term infants to < 1month

*Corrected gestational age is defined as the sum of the gestational age plus chronological age since birth.

Pediatric Patients

- 1 month to < 6 months
- 6 months to < 4 years
- 4 years to < 16 years

Number of Patients:
A sufficient number of patients to provide reasonable power (at least 80%) to detect a statistically significant difference in the primary efficacy endpoint will complete the studies. Neonatal and pediatric patients should be approximately evenly distributed between sexes. There should be reasonably equal numbers of patients in the age groups and patients should be reasonably distributed within the age ranges. A subset of randomized patients will be identified with sufficient number to characterize PK.

To ensure a sufficient number of pediatric patients will complete the PK studies, a minimum of approximately 6 patients will be needed in each of the following age groups, pre-term infants, term infants to < 1 month, 1 month to < 6 months, 6 months to < 4 years, and approximately 12 evaluable patients 4 years to < 16 years. Sample size estimates for the PK studies are based on traditional PK study design and more patients will be needed if a population PK approach is to be employed. A population PK approach is recommended, if feasible.

A sufficient number of pediatric patients of both sexes will complete the remaining studies to adequately characterize the safety of the study drug at clinically relevant doses. This should include a minimum of approximately 30 evaluable subjects in each of the following age groups, pre-term infants, term infants to < 1 month, 1 month to < 6 months, 6 months to < 4 years, and approximately 60 evaluable patients 4 years to < 16 years.

Entry Criteria:

- Pediatric patients of both sexes with moderate-to-severe pain, based on validated, age-appropriate pain scale assessments, who require treatment with an opioid analgesic will be included in these studies.

- Pediatric patients receiving neuromuscular paralytic agents and patients with neuromuscular disease, significant renal impairment (protocol defined), or significant hepatic impairment (protocol defined) will be excluded from these studies. Infants of substance-abusing mothers, infants of diabetic mothers, and infants with spina bifida will also be excluded from these studies.

Assessment Parameters:

1. Pharmacokinetic:

A subset of randomized pediatric patients in sufficient numbers to characterize the PK parameters of morphine and its primary metabolites at steady-state such as T_{max}, $t_{1/2}$, C_{max}, AUC_{ss}, Css (average steady-state concentration with multiple dosing), K_e (elimination rate constant), V_d (volume of distribution), and clearance (CL) will be studied. Adequate rationale for excluding any of the aforementioned PK parameters must be provided in the protocol. The subset of patients for PK evaluation should be representative of the larger study population with respect to age and gender. Either a traditional PK or population PK approach may be used.

- Measurement of morphine protein binding.
- Measurement of the morphine metabolites, M6G and M3G, in both urine and plasma samples at regular intervals during the study will be determined.
- Assessment of analgesia will be recorded at the time points when blood samples are taken for PK/PD correlation. In addition, as feasible, samples will be taken at intervals when dose adjustments are required due to inadequate analgesia or adverse events.

2. Clinical Efficacy:

It is essential to identify a single primary efficacy outcome reflecting adequacy of analgesia.

- Clinical assessments will be made using validated age-appropriate instruments. Inter-rater variability will be evaluated. Evaluation will include assessments by masked caretakers and assessors. The protocol will provide rationale for the choice of pain assessment instruments.

Secondary efficacy parameters will include:

- Duration of analgesic effect
- Incidence of inadequate analgesia or oversedation
- Patient discontinuation secondary to inadequate analgesia
- Time to rescue
- Amount of rescue
- Time to adequate analgesia
- Number of days required (as appropriate) for mechanical ventilation, continuous positive airway pressure or oxygen therapy, duration of intensive care or hospital stay

3. Short-term Safety

- Withdrawal signs/symptoms
- Sedation
- Incidence of adverse events (pre-term infants will also be assessed for comorbidities of prematurity such as IVH, PVL, CLD, NEC, sepsis, and PDA.)
- Vital signs (HR, BP, RR, pulse oximetry, EKG. These signs will be collected to capture potential respiratory and hemodynamic consequences associated with initiation of analgesia, changes in dose, and/or administration of bolus doses.)
- Incidence of rash
- Urine output
- GI intolerance/constipation

- Fluid volumes administered in delivering morphine
- Use of adjunct medications
- Use of rescue medications
- Total dose as a function of time (tolerance)

4. **Long-Term Safety:**

- Neurologic, behavioral, and neurocognitive developmental outcomes as assessed by pre-specified and validated age-appropriate instruments

All protocols will document any painful interventions that may affect study assessments. The extent to which comfort measures are employed and the patient's response to handling or other stimuli will be recorded and evaluated. All protocols will specify that the instruments chosen to evaluate pain in pediatric patient population subsets will be uniform among study centers.

Statistical Information, Including Power of Study and Statistical Assessments:
These studies must have a pre-specified detailed statistical analysis plan appropriate to the study design and outcome measures. The studies will be designed to provide at least 80% statistical power to detect a treatment effect, at a conventional statistical significance (p=0.05). The demographic and safety data will be tabulated and descriptive analysis of safety data will be provided. Descriptive analysis of the PK data must also be provided. A clinically meaningful effect size will be pre-specified and justified in the protocol. It will be discussed with the FDA and agreed upon prior to initiation of studies.

Drug Information (Parts I and II):
Dosage form: Approved intravenous formulation
Route of administration: Intravenous
Regimen: Bolus and continuous infusion

Bolus dose: Initial dosing in single-dose studies will be guided by the literature or current medical practice. Subsequent doses will be given according to criteria established in the protocol and based on assessments of adequacy of analgesia. The characteristics of the bolus (dose in mg/kg, duration of bolus period) should be pre-specified in the protocol and recorded in the CRF.

Continuous infusion: Infusion dosing will be set by protocol, as will the criteria and manner by which infusion doses will be adjusted. The dosing regimen will be justified by available PK/PD data, in addition to any other available information.

The studies must record and capture duration of bolus and continuous infusion dosing for all patients.

Clinical criteria for rescue dosing, escalation, or reduction of dosing will be the same in all arms of the study. Changes in dose or use of rescue doses will be based on the results of regularly scheduled assessments and on unscheduled assessments during the course of patient care and as the need arises. Assessments will consider factors including analgesia and hemodynamic endpoints.

Safety Concerns (Parts I and II):
Adverse event monitoring should include, at a minimum, the following:
- Respiratory depression
- Bradycardia

- Sedation
- Hypotension
- Appropriate clinical laboratory assessments
- Comorbidities of prematurity should be assessed as appropriate (such as IVH, PVL, CLD, NEC, sepsis, and PDA)

Individual study discontinuation criteria will be specified in protocols submitted for all studies. A Data Safety Monitoring Board with pre-specified study stopping rules shall be included in all studies.

Labeling that may result from the studies: Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of reports to be submitted: 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.

Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before March 31, 2005. 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.

Please 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. Please 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 new drug application (NDA) or as a supplement to an 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.

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.

If you have any questions, call Lisa Basham-Cruz, Regulatory Project Manager, at (301) 827-7420.

Sincerely,

{See appended electronic signature page}

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