DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-118

Baxter Healthcare Corporation
Anesthesia & Critical Care
95 Spring Street
New Providence, N.J. 07974

WRITTEN REQUEST

Attention: Priya Jambhekar
Director-Regulatory Affairs

Dear Ms. Jambhekar:

Reference is made to your Proposed Pediatric Study Request submitted on September 21, 2001, for Suprane (desflurane, USP) Liquid for Inhalation to NDA 20-118.

To obtain needed pediatric information on desflurane, 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:

***Type of studies*:**
Study 1: At least one double-blind, randomized, parallel, active control, multi-center study(ies) in pediatric surgical patients, 2 to 16 years of age, undergoing maintenance of anesthesia using mask or laryngeal mask airway (LMA) where the overall procedure time is expected to be at least 30 minutes. This study or studies will be conducted first.

Regimen:

- Pre-anesthetic medications will be standardized, and anesthesia will be induced by mask (sevoflurane) or administration of an intravenous anesthetic when an IV is available. Induction technique(s) will be standardized.
- Cases in which ventilation is predominantly spontaneous, assisted, or controlled should all be included in the study, and the mode of ventilation should be pre-specified prior to induction in each case.
- Cases of both awake and deep removal of LMA should be studied, and the timing of removal should be pre-specified prior to induction in each case.
- Agents used for the maintenance of anesthesia should be standardized and pre-specified, and these pre-specified criteria will not differ among the comparative arms of the study.
- Minimum MAC-contributions should be at least 50% of predicted MAC for desflurane and the active control (isoflurane). The minimum MAC-contributions should be the same for each arm of the study.

Study 2: At least one double-blind, randomized, parallel, active control, multi-center study(ies) in pediatric surgical patients, in infants (1 month up to 2 years of age) undergoing maintenance of anesthesia using mask or laryngeal mask airway (LMA) where the overall procedure time is expected to be at least 30 minutes. This study or studies will be conducted upon completion and safety analysis of Study 1.

Regimen:

- Pre-anesthetic medications will be standardized, and anesthesia will be induced by mask (sevoflurane) or administration of an intravenous anesthetic when an IV is available. Induction technique(s) will be standardized.
- Cases in which ventilation is predominantly spontaneous, assisted, or controlled should all be included in the study, and the mode of ventilation should be pre-specified prior to induction in each case.
- Cases of both awake and deep removal of LMA should be studied, and the timing of removal should be pre-specified prior to induction in each case.
- Agents used for the maintenance of anesthesia should be standardized and pre-specified, and these pre-specified criteria will not differ among the comparative arms of the study.
- Minimum MAC-contributions should be at least 50% of predicted MAC for desflurane and the active control (isoflurane). The minimum MAC-contributions should be the same for each arm of the study.

Objective:
Safety of desflurane for maintenance of anesthesia in non-intubated children, with particular attention to respiratory events.

***Age group in which studies will be performed*:**
Study 1: Children 2 to 16 years of age, with an approximately equal distribution of ages in this range, for each treatment group. At least 300 patients will be treated in the desflurane arm and complete the study. An equal number of patients may be treated in the isoflurane arm, or the randomization may be unequal in a proportion up to 3:1.

Study 2: Infants (1 month up to <2 years of age), with an approximately equal distribution of ages within this range for each treatment group. At least of 100 patients will be treated in the desflurane arm and complete the study. An equal number of patients may be treated in the isoflurane arm, or the randomization may be unequal in a proportion up to 3:1.

Study endpoints:

- Overall incidence of patients suffering one or more major respiratory complication(s) during maintenance, emergence, and Phase I recovery.
- Incidence of major and minor respiratory complication(s)
- Overall incidence of patients suffering one or more minor respiratory complication(s)
- Distribution of respiratory complications by type, age, mode of ventilation, and timing of LMA removal.

- Adverse events. Criteria for defining perturbations in vital signs and ECG as adverse events should be pre-specified.

Drug information:
Inhaled volatile anesthetic agents: desflurane and isoflurane

***Drug specific safety concerns*:**
Suprane is currently indicated only for maintenance of anesthesia in infants and children following induction of anesthesia with other agent(s) and tracheal intubation. The safety of Suprane for maintenance of anesthesia in children who are not intubated is unknown. However, Suprane is currently NOT recommended for induction of general anesthesia in infants and children because of a high incidence of laryngospasm, coughing, breathholding, increase in secretions, and oxyhemoglobin desaturation. These respiratory adverse events will be of particular interest in this current study.

Statistical information, including power of study and statistical assessments:
As the purpose of the study is to characterize the safety of desflurane, the primary statistical methods should be descriptive. In addition, a significance test should be performed on the proportion of patients suffering one or more major respiratory complications during maintenance, emergence, and Phase I recovery.

***Labeling that may result from the study(ies)*:**
Appropriate sections of the label may be changed to incorporate the findings of the studies, including Indications, Dosage and Administration, Pediatric Use, Clinical Pharmacology, Warnings, Precautions, and Adverse Reactions. If desflurane is significantly more or less safe than the comparator, this information may be added.

***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.

Timeframe for submitting reports of the studies:
Reports of the above studies must be submitted to the Agency on or before December 31, 2004. 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.

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 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.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at 301-827-7432.

Sincerely,

{See appended electronic signature page}

John Jenkins, 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/

John Jenkins

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