Public Health Service

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

NDA 20-214

WRITTEN REQUEST
Amendment #6

Organon, Inc.
56 Livingston Avenue
Roseland, NJ 07068

Attention: Dori L. Glassner
Director, Regulatory Affairs

Dear Ms. Glassner:

Please refer to your correspondence dated December 12, 2007, requesting changes to FDA's December 31, 2001, Written Request (WR) for pediatric studies for rocuronium bromide.

We have reviewed your proposed changes and are amending the **Number of Patients and Study Endpoints** sections of the Written Request. All other terms stated in our Written Request issued on December 31, 2001, as amended by this letter and by previous amendment(s) dated July 3, 2002, June 28, 2004, June 27, 2005, March 27, 2007, and June 22, 2007, remain the same.

Number of patients:

Study 1: 180 total, approximately equally ~~divided~~ randomized among the three dosage groups, with at least 25 total patients in the birth to less than 3 months age group, also approximately equally divided among the dosage groups. At least 3 neonates (birth to less than 1 month of age) will be randomized to each dosage group. A minimum of 15 neonates are to complete the study. The minimum number of patients required for each of the efficacy endpoints will be guided by a concurrent analysis of interpatient response variability.

Study 2: 120 total, approximately equally ~~divided~~ randomized between the two treatment arms, at least ~~20~~ 10 total patients in the birth to less than 3 months age group, approximately equally divided between the treatment arms to include at least ~~5~~ 3 neonates per treatment arm. The minimum number of patients required for each of the efficacy endpoints will be guided by a concurrent analysis of interpatient response variability.

Study Endpoints

Study 1:

Efficacy: Maximum block, onset time, reappearance of T1 and T3, spontaneous recovery to 70%, 80%, and 90% T4/T1, assessment of appropriateness to initiate laryngoscopy at 60 seconds (based upon twitch and clinical criteria, unless intubation is accomplished earlier than 60 seconds), time to intubation based on pre-specified standardized twitch and clinical criteria, intubating conditions

Safety: ECG, heart rate, blood pressure, pulse oximetry, clinical assessments of histamine release following drug administration, adverse events. Significant changes in cardiovascular parameters during the study period or in ventilatory compliance during the study period should be recorded. "Significant changes" should be pre-defined and include hemodynamic or respiratory events that require pharmacologic or non-pharmacologic intervention, including altering anesthesia depth, FIO_2, or altering ventilation mode or settings. Adverse events will be monitored and recorded at least through discharge from the post-anesthetic care unit. Criteria for defining perturbations in vital signs and ECG as adverse events should be pre-specified.

Pharmacokinetics: Blood samples should be taken from patients in all age groups, including at least 10 patients less than 3 months of age. A minimum of 6 neonates will undergo blood sampling. At least 2 samples per subject should be taken: one immediately after drug administration and one just before administration of the dose to determine C_{max}, CL, and $AUC_{0-\infty}$.

Study 2:

Efficacy: Maintenance dose requirements, maximum block, time course of recovery (reappearance of T3, spontaneous recovery to 70%, 80%, and 90% T4/T1) after bolus doses or termination of infusion of Zemuron.

Safety: ECG, heart rate, blood pressure, pulse oximetry, adverse events. Clinically significant changes in cardiovascular parameters (pre-defined) or ventilatory compliance during or following drug administration should be recorded. Significant events should include hemodynamic or respiratory events that require pharmacologic or non-pharmacologic intervention, including altering anesthesia depth, FIO_2, or altering ventilation mode or settings. Adverse events should be monitored and recorded at least through discharge from the post-anesthetic care unit.

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

Pharmacokinetics: Samples should be taken from patients in all age groups, including at least 10 patients less than 3 months of age. A minimum of 6 neonates will undergo blood sampling. At least 2 samples per subject should be taken: one immediately after drug administration and one just before administration of the next dose to determine C_{max}, CL, and $AUC_{0-\infty}$.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated December 31, 2001, as amended by this letter and by previous amendment(s) dated June 28, 2004, June 27, 2005, March 27, 2007, and June 22, 2007, must be submitted to the Agency on or before January 13, 2008, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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. In addition, send a copy of the cover letter of your submission, via fax (301-827-5911) 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, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements have also been added to the complete copy of the Written Request, as amended, that is attached to this amendment.

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval), 2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice in accordance with section 505A(e)(2).

Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that rocuronium is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies).

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. 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).

Finally, please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with

the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

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

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D.
Acting Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Attachment (Complete Copy of Written Request as amended)

NDA 20-214

WRITTEN REQUEST
Amendment #6

Organon, Inc.
56 Livingston Avenue
Roseland, NJ 07068

Attention: Dori L. Glassner
Director, Regulatory Affairs

Dear Ms. Glassner:

Please refer to your correspondence dated December 12, 2007, requesting changes to FDA's December 31, 2001, Written Request (WR) for pediatric studies for rocuronium bromide.

To obtain needed pediatric information on Zemuron, 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 trials in pediatric patients described below. These studies investigate the use of Zemuron in pediatric surgical patients.

Type of studies:

Two or more studies to examine the efficacy, safety, dose response, and pharmacokinetics of Zemuron in pediatric patients undergoing general anesthesia. General anesthesia will be induced with sevoflurane, and anesthesia maintenance will utilize isoflurane as the primary agent. Neonates (birth to less than 1 month of age) for whom rapid sequence induction is indicated may have general anesthesia induced with propofol. The onset, duration, and recovery profiles of intubation, maintenance bolus, and maintenance infusion doses other than those recommended currently in the approved package insert should be studied to provide guidance for the use of Zemuron as a neuromuscular blocking agent in pediatric patients.

Study 1: A randomized, assessor-blind, dose-ranging, multicenter trial comparing the intubating conditions and time course of block for three different intubating doses (0.45 mg/mg, 0.6 mg/kg, and 1 mg/kg) of Zemuron in pediatric (including adolescent) patients under general anesthesia.

Study 2: An open label, randomized, multicenter trial to evaluate the pharmacodynamic parameters of intubation bolus, and bolus and infusion maintenance doses of Zemuron in pediatric and adolescent patients under general anesthesia.

Objectives:

The general objectives of these investigations are to:

- Evaluate the safety and effectiveness of Zemuron in pediatric patients when using sevoflurane for induction and isoflurane for maintenance of general anesthesia. In neonates requiring a rapid sequence technique, propofol may be used for induction of general anesthesia.
- Evaluate the pharmacokinetics and dose response of Zemuron in pediatric patients including those of less than 3 months of age.
- Evaluate maintenance dose requirements for Zemuron by intravenous infusion and by intermittent intravenous bolus.
- Evaluate time course of action of Zemuron after bolus maintenance doses and after the termination of maintenance infusions.

Age group in which stud(ies) should be performed:

All studies: ASA I-III pediatric patients from birth to 17 years of age.

Number of patients:

Study 1: 180 total, approximately equally randomized among the three dosage groups, with at least 25 total patients in the birth to less than 3 months age group, also approximately equally divided among the dosage groups. At least 3 neonates (birth to less than 1 month of age) will be randomized to each dosage group. A minimum of 15 neonates are to complete the study. The minimum number of patients required for each of the efficacy endpoints will be guided by a concurrent analysis of interpatient response variability.

Study 2: 120 total, approximately equally randomized between the two treatment arms, at least 10 total patients in the birth to less than 3 months age group, approximately equally divided between the treatment arms to include at least 3 neonates per treatment arm. The minimum number of patients required for each of the efficacy endpoints will be guided by a concurrent analysis of interpatient response variability.

Study Endpoints

Study 1:

Efficacy: Maximum block, onset time, reappearance of T1 and T3, spontaneous recovery to 70%, 80%, and 90% T4/T1, assessment of appropriateness to initiate laryngoscopy at 60 seconds (based upon twitch and clinical criteria, unless intubation is accomplished earlier than 60 seconds), time to intubation based on pre-specified standardized twitch and clinical criteria, intubating conditions

Safety: ECG, heart rate, blood pressure, pulse oximetry, clinical assessments of histamine release following drug administration, adverse events. Significant changes in cardiovascular parameters during the study period or in ventilatory compliance during the study period should be recorded. "Significant changes" should be pre-defined and include hemodynamic or respiratory events that require pharmacologic or non-pharmacologic intervention, including altering anesthesia depth, FIO_2, or altering ventilation mode or settings. Adverse events will be monitored and recorded at least through discharge from the post-anesthetic care unit. Criteria for defining perturbations in vital signs and ECG as adverse events should be pre-specified.

Pharmacokinetics: Blood samples should be taken from patients in all age groups, including at least 10 patients less than 3 months of age. A minimum of 6 neonates will undergo blood sampling. At least 2 samples per subject should be taken: one immediately after drug administration and one just before administration of the dose to determine C_{max}, CL, and $AUC_{0-\infty}$.

Study 2:

Efficacy: Maintenance dose requirements, maximum block, time course of recovery (reappearance of T3, spontaneous recovery to 70%, 80%, and 90% T4/T1) after bolus doses or termination of infusion of Zemuron.

Safety: ECG, heart rate, blood pressure, pulse oximetry, adverse events. Clinically significant changes in cardiovascular parameters (pre-defined) or ventilatory compliance during or following drug administration should be recorded. Significant events should include hemodynamic or respiratory events that require pharmacologic or non-pharmacologic intervention, including altering anesthesia depth, FIO_2, or altering ventilation mode or settings. Adverse events should be monitored and recorded at least through discharge from the post-anesthetic care unit.

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Drug information :

Dosage form: Zemuron 10 mg/mL (Marketed product),

Dose: 0.45, 0.6, or 1 mg/kg

Route of administration: IV

Regimen:

Study 1:

After induction of anesthesia with N_2O/O_2 and sevoflurane (in neonates requiring rapid sequence induction, propofol may be used for induction instead of sevoflurane/nitrous oxide), isoflurane and nitrous oxide concentrations should be stabilized within a prespecified range of concentrations that will be standardized for all patients. Anesthetic concentrations should be maintained in this range for the duration of time that pharmacodynamic parameters are measured. This range should not exceed a span of greater than +0.2% end tidal isoflurane. Following stabilization, the device for assessment of the degree of neuromuscular blockade should be calibrated, and the assigned intubating dose of Zemuron will be administered as a rapid bolus.

Study 2:

After induction of anesthesia, isoflurane and nitrous oxide concentrations should be stabilized within a prespecified range of concentrations that will be standardized for all patients. Anesthetic concentrations will be maintained in this range for the entire duration of time that pharmacodynamic parameters are measured. This range should not exceed a span of greater than +0.2% end tidal isoflurane. Following stabilization, the device for assessment of the degree of neuromuscular blockade will be calibrated, and a standard dose of Zemuron should be administered as a rapid bolus. Adjunctive anesthetics (e.g., propofol, narcotics, thiopental, and benzodiazepines) may be given within pre-specified dose ranges as appropriate to provide optimal care.

Patients randomized to the bolus group will receive standardized Zemuron bolus doses at the reappearance of T3. Patients randomized to the continuous infusion group will have the Zemuron infusion begun at reappearance of T2 and titrated to maintain one or two twitches according to a pre-specified protocol. The protocol would call for assessment of neuromuscular blockage at fixed time intervals, with mandatory adjustments of the infusion rate in pre-specified increments according to the assessment result.

Statistical information, including power of study and statistical assessments:

Descriptive statistics will be presented by age and dose.

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. This report should conform with the *Guideline for Format and Content of Clinical and Statistical Sections of New Drug Applications* (July 1988) and ICH E3, *Structure and Content of Clinical Study Reports* (July 1996).

Timeframe for submitting reports of the study(ies):

Reports of the above studies must be submitted to the Agency on or before January 13, 2008, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act. Please keep in mind that pediatric exclusivity attaches 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.

Submit reports of the studies as a **supplement to an approved NDA** with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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. In addition, send a copy of the cover letter of your submission, via fax (301-827-5911) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

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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 to the pediatric population.

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

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D.
Acting 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/

Curtis Rosebraugh
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