CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20984

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-984

AUG 18 1999

Organon, Inc.
375 Mount Pleasant Avenue
West Orange, New Jersey 07502

Attention: Albert P. Mayo
Director, Regulatory Affairs

Dear Mr. Mayo:

Please refer to your New Drug Application (NDA) dated June 24, 1998, received June 25, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Raplon (rapacuronium bromide) for injection, 100 mg/5mL, 200 mg/10mL vial.

We acknowledge receipt of your submissions dated May 20, June 17 and 22, July 2 and 8, and August 13 and 18, 1999.

Your submission of June 17, 1999, received June 18, 1999, constituted a complete response to our April 22, 1999, action letter.

This new drug application provides for the use of Raplon (rapacuronium bromide) for Injection for outpatients and inpatients as an adjunct to general anesthesia to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgical procedures.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted August 18, 1999, immediate container and carton labels submitted September 1, 1998, and February 23, 1999, revised per your submission dated August 18, 1999). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL

for approved NDA 20-984." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submission dated August 13, 1999. These commitments, along with the completion dates agreed upon, are listed below.

1. Conduct single- and multiple-dose toxicity studies of rapacuronium bromide in an appropriate juvenile animal model to evaluate, in addition to the standard toxicology parameters, the effects on pituitary function, growth, and functional development. Also, data for the time course of tissue distribution should be generated in juvenile animals.

   Protocol Submission: Within 6 months following approval
   Study Start: Within 10 months following approval
   Final Report Submission: Within 18 months following approval

2. Conduct a clinical study to evaluate the time for complete excretion of rapacuronium bromide and the 3-hydroxy metabolite in the pediatric population relative to adults. At the minimum, evaluation should be carried out for the time period for complete elimination estimated from adult excretion data. If measurable levels of drug(s) are detected at this point, evaluation should be carried out until no further levels are detected.

   Protocol Submission: Within 6 months following approval
   Study Start: Within 9 months following approval
   Final Report Submission: Within 18 months following approval

3. Conduct an open-label clinical trial to evaluate the safety of Raplon™ (rapacuronium bromide) for injection given by multiple sequential bolus dosing, up to three doses. The study should enroll a minimum of 300 patients and evaluate the safety of multiple-dose bolus administration, including duration of block following each multiple dose; adverse events, particularly histamine effects; and relapse in neuromuscular function.

   Protocol Submission: Within 6 months following approval
   Study Start: Within 12 months following approval
   Final Report Submission: Within 24 months following approval

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report

to this NDA. The status summary should include the number of patients entered into each clinical study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments should be clearly designated "Phase 4 Commitments."

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until August 18, 2001. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at *www.fda.gov/cder/pediatric*) for details. If you wish to qualify for pediatric exclusivity, you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity [NOTE: You should still submit a pediatric drug development plan] and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Anesthetic,

Critical Care, and Addiction Drug Products, HFD-170, and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Susmita Samanta, Regulatory Project Manager, at (301) 827-7410.

Sincerely,

/S/

John K. Jenkins, M.D., F.C.C.P.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

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APPLICATION NUMBER: NDA 20984

APPROVABLE LETTER

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NDA 20-984

Food and Drug Administration
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Attention: Albert P. Mayo
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APR 22 1999

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We acknowledge receipt of your submissions dated September 1, 3, 14, 15 and 24, 1998, October 16 and 26, 1998, February 10, 23, 24 and 25, 1999, March 3, 9 and 26, 1999 and April 1, 5 and 15, 1999.

We have completed the review of this application and it is approvable. Before this application may be approved, however, it will be necessary for you to:

1) Revise the impurity specifications to no more than % for ORG-9488 and no more than % for total impurities.

2) Submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert). Immediate container and carton labels should be changed accordingly.

Please submit 20 copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Susmita Samanta, Regulatory Project Manager, at 301-827-7410.

Sincerely,

Victor F. Raczkowski, M.D., M.S.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure