

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20984**

**CORRESPONDENCE**

**CONFIDENTIAL**



August 13, 1999

Organon Inc.

Cynthia McCormick, M.D., Director  
Division of Anesthetic, Critical Care, and Drug Addiction Products, HFD-170  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
Document Control Room 9B23  
5600 Fishers Lane  
Rockville, Maryland 20857

NDA No. 20-984  
Raplon™ (rapacuronium bromide) for Injection  
General Correspondence: Phase 4 Commitments

Dear Dr. McCormick:

Reference is made to our New Drug Application for Raplon™ (rapacuronium bromide) for Injection, NDA No. 20-984 originally submitted on June 24, 1998; to our correspondence dated April 15, 1999 which originally provided our Phase 4 commitments; to our Approvable letter dated April 22, 1999; to our June 17, 1999 response to this Approvable Letter, and to our correspondence dated July 30, 1999 which provided the revised Phase 4 commitments. Reference is also made to the teleconference of August 12, 1999 between individuals from both the Agency and Organon, at which time the timelines for submission of the protocols, start dates for the studies and submission of the final study reports for the three Phase 4 commitment were discussed.

Accordingly, we herewith submit our commitment to initiate the three studies described below in accordance with the timelines agreed upon during the August 12, 1999 teleconference. Please note all timelines are presented as the number of months following approval of NDA No. 20-984. It was also agreed during this teleconference that if changes to these timelines need to be made at a later date, the revised timelines can be discussed with the Agency at that time.

1. 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 the time course of tissue distribution data should be generated in juvenile animals.

Protocol Submission:	6 months
Study Start:	10 months
Final Report Submission:	18 months



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Cynthia McCormick, M.D., Director  
August 13, 1999  
Page 2

2. Evaluation of the time for complete excretion of rapacuronium bromide and Org 9488 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: 6 months  
Study Start: 9 months  
Final Report Submission: 18 months

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

Protocol Submission: 6 months  
Study Start: 12 months  
Final Report Submission: 24 months

Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable section of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you require additional information, please contact the undersigned at (973) 325-4617.

Sincerely,



Dori L. Glassner  
Associate Director, Regulatory Affairs

DG/cjw

FDA Form 356H  
Submitted in Duplicate  
via Federal Express Airbill No. 810494762818

cc: Dr. Susmita Samanta, Project Manager (HFD-170) via telefax



**CONFIDENTIAL**

Organon Inc.

July 30, 1999

Cynthia McCormick, M.D., Director  
Division of Anesthetic, Critical Care, and Drug Addiction Products, HFD-170  
Office of Drug Evaluation II  
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Document Control Room 9B23  
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NDA No. 20-984  
Raplon™ (rapacuronium bromide) for Injection  
General Correspondence: Phase 4 Commitments

Dear Dr. McCormick:

Reference is made to our New Drug Application for Raplon™ (rapacuronium bromide) for Injection, NDA No. 20-984 originally submitted on June 24, 1998; to our correspondence dated April 15, 1999 which originally provided our Phase 4 commitments; to our Approvable letter dated April 22, 1999; and to our June 17, 1999 response to this Approvable Letter. Reference is also made to the teleconference of July 28, 1999 between individuals from both the Agency and Organon, at which time an additional Phase 4 commitment was discussed. Finally, reference is made to the July 30, 1999 telephone conversation between the undersigned and Susmita Samanta, Project Manager, at which time the wording for this additional Phase 4 commitment was provided.

Pursuant to the above-referenced request, Organon Inc. submits herewith, our commitment to initiate the studies described below within a reasonable period of time following approval of NDA No. 20-984.

1. 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 the time course of tissue distribution data should be generated in juvenile animals.
2. Evaluation of the time for complete excretion of rapacuronium bromide and Org 9488 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.



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Cynthia McCormick, M.D., Director  
July 30, 1999  
Page 2

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

Please note that this correspondence supersedes the correspondence of April 15, 1999 which previously provided Organon's Phase 4 commitments.

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Should you require additional information, please contact the undersigned at (973) 325-4617.

Sincerely,



Dori L. Glassner  
Associate Director, Regulatory Affairs

DG/

FDA Form 356H  
Submitted in Duplicate  
via Federal Express Airbill No. 810494762612

cc: Dr. Susmita Samanta, Project Manager (HFD-170) via telefax



Organon Inc.

September 2, 1997

N-075  
GC

**CONFIDENTIAL**

Cynthia McCormick, M.D., Director  
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IND No.

General Correspondence

Dear Dr. McCormick:

Reference is made to our Investigational New Drug Application for ORG 9487 for Injection, IND originally submitted on October 31, 1994. Further reference is made to our submission dated January 22, 1997, Amendment No. 062 in which we submitted RAPLON as the tradename for the above referenced product. Reference is also made to telefax dated April 1, 1997 from Ms. Millie Wright, Project Manager (HFD-170). This telefax indicated that the Labeling and Nomenclature Committee provisionally found the proposed name RAPLON acceptable pending the submission of the United States Adopted Name (USAN).

Accordingly, we wish to inform you that rapacuronium bromide has been adopted by the USAN Council as the United States Adopted Name. Therefore, we are requesting RAPLON to be resubmitted to the Trademark Review Committee for review and approval at their next regularly scheduled meeting.

Please advise the undersigned when the proposed tradename will be discussed at the Trademark Review Committee.

Should you have any questions related to this matter, please contact the undersigned at (973) 325-4617.

Sincerely,

Dori L. Glassner  
Manager, Regulatory Affairs

DG/cjw

Attachments  
Form FDA 1571

Submitted in Triplicate  
via Certified Mail RRR No. P-484-049-856

**ORIGINAL**



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**CONFIDENTIAL**

**Organon Inc.**

August 9, 1999

Cynthia G. McCormick, M.D., Director  
Division of Anesthetic, Critical Care, and Drug Addiction Products, HFD-170  
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Center for Drug Evaluation and Research  
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NDA No. 20-984  
Raplon™ (rapacuronium bromide) for Injection  
General Correspondence

Dear Dr. McCormick:

Reference is made to our New Drug Application for Raplon™ (rapacuronium bromide) for Injection, NDA No. 20-984 originally submitted on June 24, 1998; to our Approvable letter dated April 22, 1999; and to our June 17, 1999 response to this Approvable Letter. Reference is also made to the teleconferences of July 26, 27, 28 and August 2, 1999 between representatives of Organon and the Agency to discuss the draft labeling for Raplon™. During the initial teleconference on July 26, 1999, we were informed for the first time that the Agency is adopting a new policy whereby it will move away from the use of descriptive terms, such as "rapid" and "short" to describe the onset and duration of action of neuromuscular blocking agents in the physician package insert. Rather, the Agency intends to limit the information about onset and duration of action in the labeling for neuromuscular blocking agents to that which is described quantitatively. While a request was only being made for Organon to remove the terms "rapid" and "short" from the Raplon™ package insert, it is our understanding that, sometime in the future, the Agency intends to require the labeling of all marketed neuromuscular blocking agents to be revised to eliminate such descriptive terms as well.



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August 9, 1999  
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For the reasons stated below, Organon firmly believes that the proposed removal of descriptive terms, such as "rapid" and "short", to characterize the onset and duration of action of neuromuscular blocking agents, from package insert labeling is not only contrary with the well-accepted usage of these terms in the anesthesia community (including anesthesiologists, anesthesia residents, certified nurse anesthetists and others who may administer neuromuscular blocking agents or medically manage patients under blockade) but also inconsistent with the Agency's own long standing policy with regard to the use of these terms in package insert labeling for neuromuscular blocking agents. Moreover, the introduction of Raplon™ with labeling that does not include these descriptive terms will place Raplon™ at a substantial competitive disadvantage because the playing field will not be level.

As the Agency is aware, a past controversy over the wording of neuromuscular blocking agent labeling stimulated a desire to achieve a consensus on appropriate terms to describe the action of all neuromuscular blocking agents. As a result of this controversy, the Agency developed definitions of the terms used to describe the onset and duration of action of neuromuscular blocking agents. These definitions were published in Anesthesiology (V 82, No 1, Jan 1995), the journal of the American Society of Anesthesiologists. These descriptive terms have been widely accepted and used as a point of reference for categorizing the onset and duration of action of neuromuscular blocking agents not only within the anesthesiology community, but within the Agency itself. Organon wishes to point out that the FDA approved labeling of each and every neuromuscular blocking agent that has been cleared for marketing in the United States over the past 20 years contains such descriptive terms in either the Description and/or Clinical Pharmacology section of its FDA approved package insert. Given this long history of use and the well-accepted understanding of these terms in the anesthesia community, we believe that the Agency should seek comments from both the pharmaceutical industry and the medical community before implementing a policy to eliminate the usage of these terms in all neuromuscular package inserts. Moreover, Organon is concerned that the introduction of Raplon™ with package insert labeling that does not contain any convenient reference to the categorical classification of its onset or duration of action (in accordance with definitions published in the January 1995 Anesthesiology journal) will lead to a lack of clarity among the medical community with regard to the product's onset and duration of action classification in relationship to other currently available neuromuscular blocking agents, which may adversely affect patients. This lack of clarity may also have possible legal implications, given that the inclusion of such descriptive terms (in addition to detailed quantitative data) about the onset and duration are standardly included in the physician package insert for most every neuromuscular blocking agent currently marketed in the United States.

Cynthia G. McCormick, M.D.  
August 9, 1999  
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Organon would emphasize to the Agency that the use of descriptive terms, such as "rapid" or "short", to describe the onset and duration of action in the Description section of the package insert are important information which is solely intended to supplement the detailed quantitative information about the product's onset and duration found in the Clinical Trials and Clinical Pharmacology sections of the package insert. It is important to note these terms are consistent with how neuromuscular blocking agents are clinically characterized in the medical literature. This descriptive information therefore facilitates the ability of the medical, anesthesia and pharmacy communities to quickly categorize and use neuromuscular blocking agents.

Moreover, we bring to your attention that during the End of Phase 2 meeting held on September 8, 1995, the Agency provided Organon with a copy of the definitions and reminded Organon to adhere to these descriptions of onset and duration of action during the clinical development of Raplon™. Therefore, in good faith, and in reliance on the information provided to us by the Agency, Organon adhered to the use of these terms in the clinical reports, the NDA summaries and the draft labeling included in the NDA with an expectation that the Agency's final action on our application and draft labeling would be based upon the Agency's own clear directions to us.

Lastly, should the Agency decide at some time in the future to implement a policy to remove descriptive terms that categorize the onset and duration of action of neuromuscular blocking agents from package insert labeling, we would request that the Agency take such action uniformly against all products at the same time. Organon believes that to implement such a policy against Raplon™ alone at this time is fundamentally unfair and will place Raplon™ at a substantial competitive disadvantage by not allowing Raplon™ to be on a level playing field in the anesthesia community.

In an effort to reach a compromise on this difficult situation, Organon has proposed language which takes into account the Agency's desire to use quantitative terminology, as well as Organon's desire to use the generally accepted terms of a rapid and short to describe the actions of Raplon™. This language, which we would propose to appear in the Description section of the Raplon™ labeling, is as follows:

"Raplon™ (rapacuronium bromide) for Injection is a nondepolarizing neuromuscular blocking agent with a rapid onset of less than 90 seconds and a dose dependent duration of action. The recommended dose of 1.5 mg/kg in adults has a short clinical duration of approximately 15 minutes."

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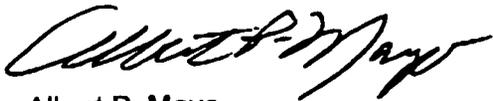
Cynthia G. McCormick, M.D.  
August 9, 1999  
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Organon believes that this is a reasonable compromise and is confident that an agreement can and should be reached quickly on this matter. Organon will, of course, continue to work constructively with the Agency in the future should it decide that it is necessary to remove descriptive terms of onset and duration of action from the package inserts of all marketed neuromuscular blocking agents. However, until the Agency moves in that direction, we believe that our proposal above satisfies both parties immediate concerns.

Organon Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable section of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you require additional information, please contact Dori Glassner at (973) 325-4617.

Sincerely,



Albert P. Mayo  
Executive Director, Regulatory Affairs

SFF:DG

Form FDA 356h

Submitted in Duplicate  
via Federal Express Airbill No. 810494762759

cc: Dr. Susmita Samanta, Project Manager (HFD-170) via telefax



April 16, 1999

Organon Inc.  
**CONFIDENTIAL**

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NDA No. 20-984  
Raplon™ (rapacuronium bromide) for Injection  
General Correspondence

Dear Dr. McCormick:

Reference is made to our New Drug Application for Raplon™ (rapacuronium bromide) for Injection, NDA No. 20-984 originally submitted on June 24, 1998. Reference is also made to the teleconference of April 13, 1999 at which time we were informed that the upcoming action letter would be an "Approval Letter" if we agreed with the labeling (package insert) that would be provided later that same day. In addition, we were informed that if more time was required to discuss the labeling, the action letter would be an "Approvable Letter".

At this time, we wish to inform you that we have reviewed the package insert provided via telefax on April 13, 1999 and are not in agreement with all of the modifications. Therefore, we are requesting additional time to reach a mutual agreement on the package insert.

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Should you require additional information, please contact Dori L. Glassner at (973) 325-4617.

Sincerely,

Albert P. Mayo  
Executive Director, Regulatory Affairs

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FDA Form 356H  
Submitted in Duplicate  
via Federal Express Airbill No. 9584252075

cc: Dr. Susmita Samanta, Project Manager (HFD-170) via telefax



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TOTAL P. 02