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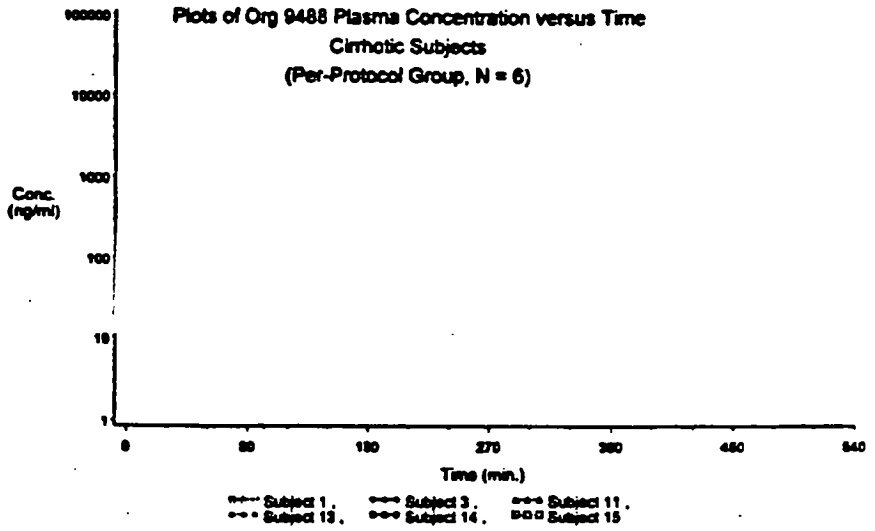
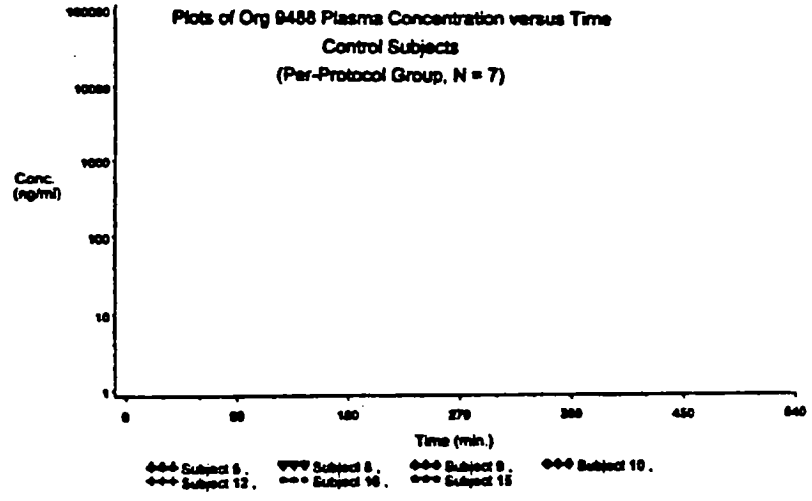
APPLICATION NUMBER: NDA 20984

ADMINISTRATIVE DOCUMENTS


Plots of Org 9488 Plasma Concentration versus Time
Cirrhotic Subjects
(Per-Protocol Group, N = 6)
Conc. (ng/ml)
1000
100
10
1
0
90
180
270
360
450
540
Time (min.)
Subject 1,
Subject 3,
Subject 11,
Subject 13,
Subject 14,
Subject 15


Plots of Org 9488 Plasma Concentration versus Time
Control Subjects
(Per-Protocol Group, N = 7)
Conc. (ng/ml)
1000
100
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1
0
90
180
270
360
450
540
Time (min.)
Subject 6,
Subject 7,
Subject 8,
Subject 9,
Subject 10,
Subject 12,
Subject 16,
Subject 18

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETICS, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS

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MEMORANDUM

to: Victor Raczkowski, MD
Acting Director, ODE III

Division File: NDA # 20-984
DFS: NDA # 20-984 (N000)

from: Cynthia McCormick, MD /S/
Director, Division of Anesthetics, Critical Care and Addiction Drug Products

subject: Raplon (rapacuronium)
Approvable Action Memo

date: April 5, 1999 4/12/99

Raplon (rapacuronium, Org 9487) is a nondepolarizing neuromuscular blocking agent which has been shown to produce its neuromuscular block (NMB) by antagonizing the action of acetylcholine at nicotinic receptors in the neuromuscular junction (NMJ) somatic nervous system. It competes for pre and post-synaptic cholinergic receptors. The drug has been professed to posses a pharmacodynamic profile that makes it competitive with succinylcholine. These features include (1) onset within 60 seconds (2) clinical duration and (3) reversibility at profound block.

COMPARISON OF FEATURES OF SOME NMBAS WITH PURPORTED FEATURES OF RAPACURONIUM

	Rapacuronium	Succinylcholine	Rocuronium	Mivacurium
Onset	"Rapid" (Sponsor's term)	"Rapid" (Sponsor's term)	Small doses give slower onset	Larger doses increase onset
Intubating conditions	Excellent to good (acceptable)@ 60 sec	Excellent at 60 sec	"	"
Clinical duration	"Short" (Sponsor's term) 25-30 minutes	"Short" (Sponsor's term) 10-15 minutes	Intermediate--30-45 minutes: Small doses give shorter duration	Large doses lengthen duration
Reversibility	Can be reversed at profound block	Can't be reversed at profound block	Can't be reversed at profound block	Can't be reversed at profound block
Other	No ↑ICP, no MH, Some histamine release	Dysrhythmias, MH, ↑ICP, ↑IOP, Prolonged effect--pts with pseudocholinesterase def		Histamine release—dose related

Dr. Rappaport has summarized the overall NDA for Raplon accurately and concisely and I agree with his conclusions. I will briefly recapitulate the basis for the Division's recommendation for approvability of this NDA.

Efficacy

The efficacy of this product has been adequately demonstrated as a neuromuscular blocking agent in single bolus administration in adequately powered and designed, active-controlled multicenter trials (baseline control implied)

using succinylcholine as the principal comparator drug. The endpoints for onset of NMB that were evaluated are the standards for this class of drugs, namely "intubating conditions" and peripheral neuromuscular block as documented by EMG. Similarly the endpoints for duration of NMB that were evaluated used several parameters, both clinical and EMG, measuring recovery of the NMJ. Complicating factors such as the contribution of anesthetic induction agents were factored into the analyses. There are two pivotal studies that were performed in support of this indication and several minor supportive studies, some of which were performed in an effort to better characterize the clinical features that the Sponsor felt were important to highlight. Dr. Cortinovis, the primary clinical reviewer for this product, has described these in detail.

There is no question, upon review of the analyses of studies 070007 and174308 that rapacuronium 1.5 mg/kg IV bolus was an effective paralyzing agent, with adequate (good plus excellent) intubating conditions achievable within 60 seconds in 87% of patients. The comparator drug, succinylcholine performed somewhat better as noted in the reviews. The non-inferiority criterion set prospectively was met for only one of these two studies.

Reversal from neuromuscular blockade was also evaluated in an N=120 Study (070010) in which reversal from Rapacuronium block (two doses, 1.5 and 2.5 mg/kg/dose) using neostigmine and placebo at set intervals and doses following administration. Recovery was assessed by EMG criteria only. This study is described in detail by Drs. Cortinovis and Rappaport and demonstrated a significantly faster recovery from complete block using neostigmine compared to spontaneous recovery, indicating that pharmacologic reversal is effective from profound rapacuronium blockade when needed.

Biopharmaceutics

Dr.Doddapaneni has done an extensive review of the clinical pharmacology and biopharmaceutics of rapacuronium with concurrence from the Office of Clinical Pharmacology and Biopharmaceutics 4/29/1999. The specific problem with prolonged excretion of this product is discussed below, under Safety.

Safety

As described, there has been adequate evaluation of the safety of rapacuronium in 2036 patients and subjects, most who received treatment with a single IV bolus.

Dose and Duration. The following table displays the overall exposure (updated at 4 months) to rapacuronium single dose and multiple dose/infusion:

TABLE 1 OVERALL EXPOSURE

Exposure	NDA	4MSU	Total
Single Dose	1666	63	1729
Multiple Dose	307	0	307
Total	1973	63	2036

As shown in the following chart of dose at initial exposure (most from patients receiving single doses), the bulk of exposure was in the range of 1.35-1.65 mg and very little in the >2.75 range.

TABLE 2 EXPOSURE BY DOSE (UPDATED) AT INITIAL EXPOSURE

Age Group	Rapacuronium Exposure (mg/kg)			
	< 1.35	1.35-1.65	1.7-2.75	>2.75
Pediatrics	161	40	123	70
Adult (18-64)	122	983	185	38
Geriatric (>65)	37	137	30	6
Total	320	1160	338	114

In the NDA there were 307 patients who received more than a single dose. This included patients who received multiple boluses and patients who received an infusion following a single IV bolus. There is insufficient acute

safety or follow-up data in these patients to allow for labeling of this type of regimen. In addition there are special safety considerations associated with this drug's slow elimination and probable accumulation which need further evaluation, and which will be detailed in this memo.

Deaths Dropouts and Serious Adverse Events, Common Adverse Events

The rare deaths reported in association with rapacuronium do not raise any special safety concerns and there were no dropouts from clinical studies. The serious adverse events that might be reasonably attributed to medication included a small number of reports of tachycardia, hypotension, pulmonary edema, cardio-respiratory arrest or apnea, bronchospasm, ileus, and urinary retention.

These were also among the most commonly reported adverse events (>2%) which included hypotension (6.1%), bronchospasm (4%), tachycardia (2.5%) which are detailed in tabular format in Dr. Cortinovis' review.

Safety—Biopharmaceutics issues

It is important to reiterate from Dr. Doddapaneni's careful review of the biopharmaceutics of rapacuronium, the findings from the mass balance study that was performed in six healthy volunteers, and to correlate these findings with those of other drugs in this class and across species to better understand one of the features of this drug that raises specific safety concerns. As Dr. Doddapaneni points out, a single center study was performed in 6 volunteers using a single IV dose of 1.5 mg/kg of [^{14}C] Org 9487 (radiolabeled rapacuronium). Blood samples were collected for 6 weeks, urine and fecal samples were collected for two weeks, and expired air samples were collected for 24 hours. Radiocarbon could be measured in all urine and fecal samples up to two weeks following a single dose. The mean combined excretion at the end of two weeks was in the range of 50-64%. The following table shows the class of aminosteroid neuromuscular blocking agents and what is known about their excretion. The older agents such as pancuronium have less information than the newer ones. They are largely excreted by the urinary and biliary routes, and are slow to be excreted.

DRUG	EXCRETION
Rapacuronium	50-64% excretion at 14 days
Pancuronium	Unknown
Pipecuronium	Unknown
Vecuronium	3-4 days to clear drug—sequestration in tissues
Rocuronium	88-94% excretion at 9 days

With all of these agents it is possible to demonstrate cumulative effect with repeated doses of drug and delayed recovery of neuromuscular function is not uncommon. However this new agent stands out among its chemical cousins in this class as one with considerably slower excretion.

Animal studies that evaluated elimination of drug across species confirms a similar profile but more rapid excretion in animals, in general, than in the human. These results are summarized below but found in more detail in Dr. Jean's review.

	% DOSE EXCRETED		
Drug	Total	Species	Time (days)
Rapacuronium	73-83	Rat	7
	66	Dog	7
	56	Human	14 days
Rocuronium	86	Rat	7
	90	Dog	7
	88-94	Human	9
Vecuronium	58	Rat	<1 (10 hr)
	40%	Dog	<1
	Complete	Human	3-4 days
Pipecuronium	51%	Rat	2 days
	79%	Dog	4 days
	unknown	Human	unknown

The disposition of drug in animal tissue is similar for rocuronium and rapicuronium, and is, one week following single dose, shown to be sequestered in kidney, heart, lung, and pituitary in small amounts. Nevertheless, following subacute dosing with rapacuronium, specific histopathologic changes in the kidney only (inflammatory changes and mineralization) were not demonstrated in animals until doses in the range of 18 mg/kg/day.

In conclusion, this slow excretion and sequestration in tissues is a known characteristic of this class of drugs, not known to be associated with specific residual safety problems in the short term following single dose. However, following multiple dose administration, infusion, and chronic administration, such problems as prolonged blockade, reversal problems, and ICU "myopathy" are notable. There have been few long-term studies of the potential toxicity to specific common sequestration sites such as bone, kidney, muscle, heart, and pituitary. There should be more care in exploring subacute or chronic toxicity with rapacuronium if ICU use is anticipated in the future, since its excretion is so much longer than the others. There are no known adverse experiences from many years' experience (relating to sequestration) of single dose exposure to the related compounds in this class. The problems that have been reported have occurred with chronic infusion or multiple dose exposure. Reassurance is gained from safe passage in humans following single dose exposure despite the absence of long term follow-up in the NDA.

Pediatrics

A total of 397 pediatric patients have been exposed to rapacuronium, single dose. The breakdown by age and by dose is as follows:

TABLE 3 PEDIATRIC EXPOSURE BY DOSE AND AGE (UPDATED)

Age Group	Rapacuronium Exposure (mg/kg)				
	< 1.35	1.35-1.65	>1.65-2.75	>2.75	Total
0-1 month	30	5	4	0	39
1 mo.- 2 years	75	15	57	31	178
2 years-12 years	56	20	62	39	177
Total	161	40	123	70	397

The majority of pediatric patients (99.5%) were ASA I and II.

The most common adverse events in the pediatric patients were respiratory and rash.

While the acute evaluation of safety following single dose administration of rapacuronium was ostensibly benign, it is known from preclinical studies and adult radioisotope studies that rapacuronium has an extended half-life following a single dose. It deposits in animals in tissues such as kidney, heart, bone, and pituitary. (See Pharmacology/Toxicology and Clinical Biopharm reviews). The half-life in pediatric patients is not known. This may have important implications in chronic dosing paradigms—not yet underway—in pediatric patients. It also remains to be seen whether prolonged deposition in certain tissues, such as pituitary or bone have any long-term effects on the developing child.

Drs Cortinovis and Rappaport have raised the question of safety of even single dose exposure to rapacuronium in children, particularly infants, including the accidental exposure to low concentrations at delivery. I have considered their concerns, namely that there may be sequestration over the short term of low doses of drug which may adversely effect development—particularly in pituitary or bone. These are reasonable concerns and good, probing questions about this product's safety profile for which we do not have absolute assurance of safety. There is, however, some reassuring data from one-month animal studies exposed to higher levels per kg. (than one would expect to see in infants and children given a single dose for surgery) that show no histologic changes in any organs. Further reassurance is gained from the pediatric use of the other aminiosteroid neuromuscular blocking agents with similar excretion characteristics, albeit not as slow. The question remains, has the Sponsor done all things applicable and reasonable to assure the safety in this population? My view is that there is not sufficient safety data in the newborn period with actual use, to justify labeling, however there is reasonable assurance that single dosing in the 1-month to 12-year population is safe.

The following questions should be addressed by the sponsor as a phase IV commitment to be completed within a year of approval: (1) preclinical studies in developmental models of toxicity to assess effects on structure and function of developing organ systems and (2) study of the rate of excretion in the pediatric population.

Specific Safety Issues:

Possible Histamine Release

Nondepolarizing neuromuscular blocking agents have the potential to elicit histamine release in exposed subjects. There was one US study (090011) in which histamine levels were obtained. Plasma samples in this N=46 study were obtained pre-induction, at induction, before administration of Org 9487 and at 1,3,5 minutes after administration of one of three doses. Clinically significant histamine levels were defined as 100% increase from baseline. Plasma histamine levels increased after Org 9487 administration in all three groups in a dose dependent fashion, peaking at 1 minute following the higher doses.

Despite this, clinically significant adverse events related to histamine release were not reported in clinical studies. Presence of events such as flushing, redness, wheals, hives and erythema were evaluated in patients receiving rapacuronium as possible histamine effects. One patient (7 month old) experienced induration at the injection site that was thought to be possibly histamine related.

Malignant hyperthermia

There were no reports of malignant hyperthermia (MH) in clinical trials involving >2000 patients receiving rapacuronium. Animal studies were also performed using three species of swine—presumed MH-negative, proven MH-negative and MH-susceptible swine. No animals developed malignant hyperthermia in any group following exposure to three increasing doses of Org 9487.

Cardiovascular Function

Org 9487 (rapacuronium) has been tested for its ability to block the effects of acetylcholine at muscarinic receptors in the heart and at nicotinic receptors in the autonomic ganglia (ANS). In humans the block of these groups of receptors can produce tachycardia and hypotension, respectively. For this reason the sponsor has done a thorough cardiovascular evaluation of this product. Dr. Jean, the toxicology team leader, carefully reviewed these herself (refer to her review).

Preclinical

In her review of preclinical pharmacology Dr.Jean discusses the effects of rapacuronium on cardiovascular function after review of a number of *in vitro* tests and *in vivo* animal studies. These evaluated the effect of rapacuronium on HR and in particular on the QT interval.

Rapacuronium produced transient mild hypotension (10-20% decreases) following 3x ED_{90} in cats, dogs, and pigs. Hypertension preceding hypotension was noted in cats. Heart rate was not significantly affected or only slight tachycardia was noted at this dose.

In dogs and cats drug related EKG changes were noted following repeat dosing totaling 40 mg/kg. These changes included prolonged QT interval, sinus arrhythmia with prolonged PR interval, widening of p-waves, and AT dissociation with accrochage in the dog, RBBB and PR prolongation in the cat. The EKG abnormalities were reversible after 2 weeks.

The acute effects on the QT-interval were studied in anesthetized pigs administered high doses (10xED_{90}) of multiple dose rapacuronium and the active metabolite ORG 9488. HR, BP and EKG were measured in these animals at .5 to10 minutes following the first two sub-doses and HR was shown to increase slightly. The HR and QTc interval showed slight decreases following the final in all groups.

In summary, in dogs and cats the LOAELs for EKG effects are 27 mg/kg. And the NOAELs are 5 subdoses of 6 mg/kg for a one-day treatment. Dose and extent and duration related hypotension were significant only at the 10x human ED_{90}.

Clinical
Clinical EKG function and vital signs were measured in all studies. There were specialized studies performed in addition, which evaluated EKG function.

In US Study 070012, pediatric patients (infants and children) were evaluated for changes in cardiovascular function. This was a two part study in which patients were dosed with rapacuronium (in part I) IM and (in part II) IM or IV. Patients were evaluated for BP, and HR, measured at 1-minute intervals for 5 minutes and at 10 minutes following administration of drug. Increases in HR were demonstrated within 3 minutes of drug administration in the range of 15-30 bpm (maximum).

In addition, as noted under the general section on adverse events, tachycardia (2.5%) and hypotension (6.1%) were reported at low frequencies, and occasionally as serious adverse events. In the serious adverse event reports there were also seven cases of cardio-respiratory arrest or apnea. Dr. Cortinovis has reviewed of these cases and has concluded that these were not primarily cardiac in origin, but rather a function of neuromuscular paralysis.

The results of the preclinical studies and human experience with rapacuronium suggest some mild effect of the drug on HR and blood pressure. At the doses used in the clinical studies these effects did not appear to pose any safety concerns. This will need to be evaluated in much more depth in the event that this drug is ever conceived for use in the ICU setting, that is, chronic repeated dosing, particularly in view of the long half-life of this product due to its protracted excretion.

ICP
There were two reports of increased intracranial pressure in the NDA. The patients were reported in Study 174304, which specifically evaluated the effects of rapacuronium on intracranial pressure. It was a placebo- and active-control (vecuronium) trial in which ICP was measured (intraventricularly) at 1-minute intervals within 10 minutes of administration of rapacuronium and at 15 minutes. It was a small study N=18, of whom 7 received rapacuronium. Both patients had suffered from traumatic brain injury.

In general the study showed no effect in the majority of patients, but two patients in the rapacuronium-treated group and one in the vecuronium-treated group demonstrated a spike in ICP up to 22 mmHg from baseline. One patient had undergone craniectomy for severe swelling and removal of a subdural hematoma. He did not receive rapacuronium until the postoperative period, and he went on to have continued cerebral edema. He died 8 days postoperatively with uncal herniation leading to cardiovascular collapse. The intracranial hypertension was more likely a function of the underlying brain injury than medication.

The other rapacuronium-treated patient who spiked two minutes following rapacuronium responded to hyperventilation and increase in his dopamine infusion. He also had been admitted to the study with a traumatic brain injury. It cannot be determined if the increase in ICP was due to the injury or related somehow to the medication. The previous pattern of ICP spikes in this patient and in the patient who had a similar experience with vecuronium was not completely known, although, as Dr. Rappaport points out, this patient had experienced a similar spike in ICP earlier the same day. More information is needed before drawing any definite conclusions about drug attribution. At this point it appears rather unlikely.

IOP
Intraocular pressure was evaluated in one non-US study, 174305, comparing the effects of rapacuronium, vecuronium and succinylcholine. Moderate decreases in IOP (in the magnitude of 15% and 18% respectively) were noted with vecuronium and rapacuronium following treatment with rapacuronium and intubation compared with a 43% increase following treatment with succinylcholine.

C-section:
The evaluation of rapacuronium in the setting of C-section delivery has been described by Dr. Cortinovis and discussed further by Dr. Rappaport. I concur with Dr. Rappaport that the outcomes (assessed by Apgars) in infants following delivery where rapacuronium is used is comparable to the control group. There is no significant cause for concern in these infants beyond the usual concerns of a delivery by C-section with general anesthesia. It is important to note that based on umbilical/maternal concentration ratio data, there is some placental transfer of rapicuronium and its metabolite, Org 9488 from maternal blood to the infant at delivery (see Dr. Doddapaneni's

EFFECTIVENESS:

Evidence of efficacy has been submitted in the clinical studies 070007, 174308, 070008, 174303, and 070010. Supportive evidence of effectiveness has been submitted in the clinical studies 174208, 070005, 174305, 070003, 174309, 070002, and 070004.

Study 070007:

This was a randomized, assessor blinded, parallel group, active-controlled, study performed at five centers in the US, which compared the effect of Raplon to succinylcholine for intubation prior to elective surgery. Patients were preoxygenated for three minutes followed by induction of anesthesia with 2 to 5 μg/kg of fentanyl, and 1 to 3 mg/kg propofol. Patients were randomized to receive either Raplon (1.5 mg/kg) or succinylcholine 1.0 mg/kg IV. Four to 5 minutes after the administration of the fentanyl, the full dose of muscle relaxant was administered as an IV bolus within a 5 second interval. Laryngoscopy was attempted at 50 seconds following the end of the administration of the muscle relaxant. Intubation was to be completed within 60 seconds. If intubation was not possible within 60 seconds, a second attempt was to be made within 90 seconds.

The primary efficacy parameter was the percentage of patients with "acceptable" intubation scores, measured as the number of patients who fell into one of four categories: excellent, good, poor or impossible. A blinded assessor evaluated and scored the intubating condition based on the following definitions:

Table 1.

	CLINICALLY ACCEPTABLE		
	Excellent	Good	Poor
Vocal Cord Position	Abducted	Intermediate	Closed
Vocal Cord Movement	None	Moving	Closing
Easiness of Laryngoscopy*	Easy	Fair	Difficult
Airway Reaction	None	Diaphragm	Sustained >10 sec
Movement of the Limbs	None	Slight	Vigorous

*Easy: Jaw relaxed; no resistance
Fair: Jaw relaxed; slight resistance

Excellent: All items excellent
Good: All items excellent or good
Poor: Any item poor

The scores were than collapsed into "acceptable", consisting of excellent and good, or "not-acceptable", consisting of poor and impossible.

The protocol defined a non-inferiority criterion of no more than a 10 % difference with 95 % confidence (one-sided).

The following secondary efficacy endpoints were recorded and analyzed in order to evaluate by electromechanomyography [EMG], in a Train of Four [TOF] Guard calibrated fashion, the time course of action of the study drug[1]:

- Time to reappearance of the first twitch (to 25% of its baseline); representing duration of neuromuscular blockade;
- Time to reappearance of the third twitch (Raplon subjects only); alternative representation of the duration of neuromuscular blockade
- Time to T4/T1 ratio recovery to 0.7 (Raplon subjects only)
- Time to T1 = 90% of the final T1
- Time to full recovery from muscle relaxation; for all subjects this is defined as the first time at which there are no further increases in the height of the twitches for a period of about five minutes
- Clinical signs of recovery (head lift, hand squeeze, tongue extension) were also recorded.

[1] The ulnar nerve is stimulated with four shocks over 1.5 seconds. Four distinct twitches are produced and designated T1 through T4. Increasing neuromuscular blockade results in loss of the last three twitches and reduction in the magnitude of T1. This reduction in magnitude can be measured by the force the thumb exerts.

Results:

The following table copied from Dr. Cortinovis' review [p. 19, Table 4], summarizes the patient disposition for this study:

Table 2.

Subject Data Set	Treatment Group						
	Org 9487 (1.5mg/kg)			Succinylcholine (1.0 mg/kg)			
	Adult	Geriatric	Total	Adult	Geriatric	Total	TOTAL
Total Randomized	133	37	170	131	36	167	337
All Subject Treated *	133	36	169	131	36	167	336*
Intent to Treat	133	36	169	131	36	167	336
Per Protocol	98	26	124	84	28	112	236

* ITT Group excluded one subject: Subject # 573 was discontinued from the study prior to administration of study drug but due to equipment problems the study was abandoned and the subject did not receive study medication

The protocol called for 56 subjects to be enrolled at each of the five sites. This was amended during the trial to allow the additional enrollment of 14 patients per center. This was because a large number of patients were excluded due to protocol violations, (primarily a prolonged time between fentanyl/propofol administration and muscle relaxant administration), at one of the five centers. The additional patients were enrolled at the other four centers.

The following table, based on Dr. Cortinovis' Table 6 , page 21 of his review, summarizes the major protocol violations:

Table 3.

MAJOR PROTOCOL VIOLATIONS				
Protocol Violation	Treatment Group			
	Org 9487 Subjects per site		Succinylcholine (1.0 mg/kg) Subjects	
FAIL TO FOLLOW RANDOMIZATION SCHEDULE	Site 1	1	Site 1	
	Site 2		Site 2	
	Site 3		Site 3	
	Site 4		Site 4	
	Site 5	1	Site 5	
"YES" TO INCLUSION/EXCLUSION	Site 1	1	Site 1	
	Site 2		Site 2	1
	Site 3		Site 3	
	Site 4		Site 4	
	Site 5	1	Site 5	
TIME FROM FENTANYL ADMINISTRATION TO MUSCLE RELAXANT GREATER THAN 6 MINUTES	Site 1	17	Site 1	18
	Site 2		Site 2	
	Site 3	1	Site 3	4
	Site 4	2	Site 4	4
	Site 5	8	Site 5	8
TIME FROM PROPOFOL ADMINISTRATION TO MUSCLE ADMINISTRATION GREATER THAN 3 MINUTES	Site 1	27	Site 1	26
	Site 2		Site 2	1
	Site 3		Site 3	
	Site 4		Site 4	3
	Site 5		Site 5	2
LIDOCAINE ≥ 50 MG TO FACILITATE INTUBATION	Site 1		Site 1	
	Site 2		Site 2	
	Site 3		Site 3	
	Site 4	1	Site 4	5
	Site 5	4	Site 5	1
TOTAL	45		55	

Treatment groups appeared to be generally matched on relevant measures at baseline.

Primary Efficacy Analyses:

The intubation scores are summarized in the following table copied from Dr. Cortinovis' Table 10 on page 25 of his review:

Table 4.

	PER PROTOCOL GROUP		ITT GROUP	
	Org 9487 (%)	Succinylcholine (%)	Org 9487 (%)	Succinylcholine (%)
Acceptable [Acceptable = Excellent + Good]	108/124 (87)	106/112 (95)	148/169 (88)	157/167 (94)
Excellent	53/124 (43)	74/112 (66)	75/169 (44)	110/167 (66)
Good	55/124 (44)	32/112 (29)	73/169 (43)	47/167 (28)

The intubation scores for the Per Protocol[2] group, broken down by age category, are summarized in the following table copied from Dr. Cortinovis' Table 11 on page 25 of his review:

Table 5.

	AGE GROUP (PER PROTOCOL)			
	ADULT		GERIATRIC	
	Treatment Group		Treatment Group	
	Org 9487 1.5mg/kg N=98 (%)	Succinylcholine 1.0 mg/kg N=84 (%)	Org 9487 1.5 mg/kg N=26 (%)	Succinylcholine 1.0 mg/kg N=28 (%)
Excellent	40 (41)	52 (62)	13 (50)	22 (79)
Good	43 (44)	26 (31)	12 (46)	6 (21)
Poor	15 (15)	4 (5)	1 (4)	0
Impossible	0	2 (2)	0	0
Acceptable	83 (85)	78 (93)	25 (96)	28 (100)
Unacceptable	15 (15)	6 (7)	1 (4)	0

The protocol defined noninferiority criterion of no more than 10% difference with 95% confidence (one-sided) was not met, and there were obvious differences in the distributions of acceptable conditions between excellent and good.

[2] As per Dr. Permutt: "The applicant argues that a longer interval [between administration of fentanyl and of the blocking agent] can affect the intubating conditions, and therefore considers the per-protocol analysis more informative than the intent-to-treat analysis...I agree that there is no reason to think the intent-to-treat analysis would be less subject to bias."

Secondary Efficacy Measures:

The results of the EMG measurements of duration and recovery for the two treatment groups are summarized in the following table, copied from Dr. Cortinovis' Table 12, page 27 of his review.

Table 6.

Parameter	Treatment Group	
	Org 9487	SUCCINYLCHOLINE
Time to Return of 3rd Twitch		
N	94	NA
Mean ± SD	14.1 (6.2)	
95% CI	12.8-15.3	
Median	13.1	
Range	5.2-32.5	
Duration to 70% T4/T1		
N	77	NA
Mean ± SD	37 (14.5)	
95% CI	33.7-40.3	
Median	34.2	
Range	13.8-97.3	
Duration to 90% T1		
N	38	27
Mean ± SD	32.9 (10.6)	12.3 (4.7)
95% CI	29.4-36.4	10.4-14.2
Median	30	11.8
Range	14.7-64.3	4.8-28.2
Time to Full Recovery		
N	34	39
Mean ± SD	46.5 (17)	15.1 (6.6)
Median	42.3	13.8
Range	23.3-90.2	4-31.7

Study 174308:

This was a randomized, assessor blinded, parallel group, active-controlled, study performed at four centers in France which compared the effect of Raplon to succinylcholine for intubation prior to elective surgery. Patients were preoxygenated for three minutes followed by induction of anesthesia with 2 to 3 μg/kg of fentanyl, 3 to 6 mg/kg thiopental, and inhalation of nitrous oxide in oxygen at the discretion of the anesthesiologist. Patients were randomized to receive either Raplon 1.5 mg/kg IV or succinylcholine 1.0 mg/kg IV. Laryngoscopy was attempted at 50 seconds following the end of the administration of the muscle relaxant. Intubation was to be completed within

60 seconds. If intubation was not possible within 60 seconds, a second attempt was to be made within 90 seconds.

The primary efficacy parameter was the intubating condition provided by the muscle relaxant, measured as the number of patients who fell into one of three categories: excellent, good or poor. A blinded assessor evaluated and scored the intubating condition based on the definitions described above in Study 070007.

The protocol defined a non-inferiority criterion of no more than a 10 % difference with 95 % confidence (one-sided).

The following secondary efficacy endpoints were recorded and analyzed in order to evaluate by electromechanomyography [EMG], in a Train of Four [TOF] Guard calibrated fashion, the time course of action of the study drug:

- Time to reappearance of the first twitch (to 25% of its baseline); representing duration of neuromuscular blockade;
- Time to reappearance of the third twitch (Raplon subjects only); alternative representation of the duration of neuromuscular blockade
- Time to T4/T1 ratio recovery to 0.7 (Raplon subjects only)
- Time to T1 = 90% of the final T1
- Time to full recovery from muscle relaxation; for Raplon subjects this is defined as the time to a TOF ratio over 0.80, which remains at least 0.80 on the following two measurements; for succinylcholine subjects it is defined as the time after which there is no or very little increase in the height of the twitches for a period of about two minutes

Clinical signs of recovery (head lift, hand squeeze, tongue extension) were also recorded, but only in subjects who received a single dose of muscle relaxant.

Results:

The following table copied from Dr. Cortinovis' review [p. 36, Table 15], summarizes the patient disposition for this study:

Table 7.

	Number of Subjects				
	Treatment Group				Total
	Org 9487		Succinylcholine		
	Adults	Geriatrics	Adults	Geriatrics	
All Subjects Randomized	113	30	112	28	283
Intent to Treat	112	30	112	28	282
Per Protocol	107	26	106	27	266

An additional five patients per treatment group were eliminated from analysis. Three had missing primary data and the other seven had anatomical malformations making intubation impossible under the trial conditions. Based on amendment 3 to the original protocol [see Dr. Cortinovis' review, p. 35], 22 patients were scored by empirical evaluation rather then the criteria noted above. Twelve of the patients received Raplon and 10 received succinylcholine.

Treatment groups appeared to be generally matched on relevant measures at baseline.

Primary Efficacy Analyses:

The intubation conditions are summarized for the Per Protocol group in Dr. Cortinovis' Table 22 on page 42 of his review. The intubation scores for the Per Protocol group are summarized in the following table copied from Dr. Cortinovis' Table 23 on page 42 of his review:

Table 8.

Intubation Score	Treatment Group			
	Org 9487		Succinylcholine	
	N[1]	%	N[2]	%
Excellent	39	30.5	61	47.7
Good	71	55.5	52	40.6
Poor	11	8.6	12	9.4
Impossible	7	5.5	3	2.3

A large number of protocol violations, including errors in recording procedures and equipment failure, make interpretation of this data difficult at best.

Study 070008:

This was a randomized, parallel group, open label, study performed at three centers in the US, which compared the time course of neuromuscular blockade for intubation (for elective surgery) between two different doses (1 mg/kg and 2 mg/kg) of Raplon in subjects less than two years of age, and two different doses (2 mg/kg and 3 mg/kg) of Raplon and one dose (0.2 mg/kg) of mivacurium in children over 2 and under 13 years of age.

Neonates were treated with atropine followed by nitrous oxide in O_2 and halothane. One hundred percent O_2 was used for intubation. Adjustments were allowed on a prn basis. Children 29 days or older and up to 13 years of age were induced with nitrous oxide in O_2 and halothane. Muscle relaxants were administered after stabilization of anesthesia and hemodynamics, and after three stable TOF responses. All subjects were maintained on halothane. The randomly assigned dose of neuromuscular blocker was then administered as a bolus over 5 seconds, or as clinically indicated. Neonates were intubated after a two minute cardiovascular measurement period which followed administration of the muscle relaxant. The older children were intubated after a three minute cardiovascular measurement period following muscle relaxant administration. Anesthesia was maintained for all patients with nitrous oxide and halothane.

If additional muscle relaxant was needed during the surgical period, a neuromuscular blocking agent other than the study drugs was used. Subjects were allowed to spontaneously recover to 70% T4/T1, whenever possible.

The primary efficacy parameters were the T1 (degree of neuromuscular blockade) at 60 seconds post-intubation as a percent of the control (measured prior to blockade) T1, and the clinical duration of neuromuscular blockade, measured as the time interval between drug administration and return to 25% of the control T1.

The following secondary efficacy endpoints were recorded and analyzed:

- Onset Time, defined as the time interval between completion of the injection of the study drug and the time of maximal depression of the TOF;
- Maximal Block (Peak Effect), defined as the first T1 which shows no further decline over three consecutive TOF's following administration of study drug;
- Recovery Rate, defined as recovery of 24% to 75% of the control T1;

Treatment groups appeared to be generally matched on relevant measures at baseline.

Primary Efficacy Analyses:

The T1 measurements at 60 seconds are summarized in the following table copied from Dr. Cortinovis' Table 30 on page 54 of his review:

Table 13.

Statistic	Age/Treatment Group						
	Neonates <29 days		Children ≥ 29 days to < 2 years		Children ≥ 2 years to <13 years		
	Org 9487 Mg/kg		Org 9487 Mg/kg		Org 9487 Mg/kg		Mivacurium Mg/kg
	1.0	2.0	1.0	2.0	2.0	3.0	0.2
N	5	4	14	16	23	21[a]	22[b]
Mean ± SD % of Control T1	5.2 ± 9.6	7.6 ± 13.6	9.2 ± 16.9	7.6± 21.8	1.0 ± 2.3	5.4 ± 17.5	48.9 ± 40.9
Median % of Control T1	0	1.3	1.5	0	0	0	52
Min-Max	0-22	0-28	0-56	0-88	0-8	0-80	0-142

a One subject did not have T1 at 60 sec due to an artifact on EMG. Another subject did not have T1 recorded due to a procedural error

b One subject did not have T1 at 60 sec due to a problem on EMG

The differences between the Raplon dose group results within the age categories were not statistically significant, $p = 0.99$ and 0.33, for the neonate and children 29 days to 2 years groups, respectively. Both Raplon dosages resulted in statistically significantly lower percents of the control T1's compared to mivacurium ($p < 0.01$).

The clinical duration scores for the Per Protocol group, broken down by age category, are summarized in the following table copied from Dr. Cortinovis' Table 31 on page 55 of his review:

Table 14. Time from end of drug administration to return to 25% of the control T1

Statistic	Age/Treatment Group						
	Neonates <29 days		Children ≥29 days to < 2 years		Children ≥2 years to <13 years		
	Org 9487 Mg/kg		Org 9487 Mg/kg		Org 9487 Mg/kg		Mivacurium Mg/kg
	1.0	2.0	1.0	2.0	2.0	3.0	0.2
N	4	4	13	16	23	20	23
Mean ± SD minutes	9.8 ± 3.1	13.5 ± 2.8	9.2 ± 2.6	16.1 ± 7	13.8 ± 7.2	17.8 ± 3.2	10.3 ± 3
Median minutes	9.7	13.4	9.4	14.7	12.7	17.4	9.5
Min-Max	6-13.7	10.3-16.8	5.5-13	1.7-32.4	8.5-44.2	11.5-23.6	4.6-14.9

Clinical duration was not measured for one subject in the neonate group, one subject in the <2 year old group, and three subjects in the Raplon >2 year old group.

Statistically significant differences were found for the two doses of Raplon versus mivacurium ($p < 0.01$ and $p = 0.03$, for the 3.0 and 2.0 mg/kg doses, respectively), as well as for the 2.0 mg/kg versus the 1.0 mg/kg groups in the children less than two years group ($p < 0.01$).

Secondary Efficacy Measures:

The results of the EMG measurements of duration and recovery for the two treatment groups are summarized in the following table, copied from Dr. Cortinovis' Table 32, page 56 of his review.

Table 15.

Statistical Parameter	Neonates (< 29 days)		Children (≥ 29 days to < 2 years)		Children (≥ 2 years to < 13 years)		
	Org 9487 (mg/kg)		Org 9487 (mg/kg)		Org 9487 (mg/kg)		Mivacurium Chloride (mg/kg)
	1.0	2.0	1.0	2.0	2.0	3.0	0.2
Peak Effect (T1, % of Control)							
N	5	4	14	16	23	21 [a]	23
Mean ± SD	1.1±2.4	3.3±6.5	4.4±12.4	0.8±3.0	0.3±1.3	0.2±1.9	1.5±4.2
Median	0	0	0	0	0	0	0
Min -Max	0-5.4	0-13.0	0-46.0	0-12.0	0-6.0	0-4.0	0-20.0
Onset Time (seconds)							
N[a]	5	4	14	16	23	21 [a]	22
Mean ± SD	98±95	190±261	88±73	84±66	53±16	67±44	155±92
Median	39	75	73	55	50	59	140
Min - Max	20-220	30-580	20-300	20-250	32-100	10-228	50-460
Recovery Rate from 25% to 75% T1 (Minutes)							
N[b]	1	1	9	8	19	12	15
Mean ± SD	7.5	4.0	6.9±3.9	13.4±10.8	6.3±3.9	11.1±6.2	3.8±1.1
Median	7.5	4.0	5.6	9.5	5.3	9.5	3.7
Min - Max	7.5-7.5	4.0-4.0	3.0-15.1	4.0-37.0	2.5-18.3	4.7-24.5	2.6-6.3
Duration to 70% T4/T1 (Minutes)[c]							
N	4	4	12	16	21	19	22
Mean ± SD	25.0±10.9	22.8±5.9	19.5±6.9	34.3±13.2	25.5±9.1	37.1±9.4	16.2±3.9
Median	21.3	23.0	18.1	29.3	22.6	34.0	15.4
Min - Max	16.5-41.0	16.5-28.7	10.7-29.9	17.5-67.9	17.5-50.5	22.5-54.2	9.4-23.9

The median Onset Time for Raplon was approximately one minute compared to greater than two minutes for mivacurium; although the range was quite wide. Recovery and duration were generally longer for Raplon compared to mivacurium

Study 174303:

This was a randomized, assessor blinded, parallel group, active-controlled, study performed at five centers in Germany and Austria, which compared the effect of Raplon to succinylcholine on intubating conditions for elective, rapid sequence induction. Normal body weight and obese patients were recruited. Due to difficulty with recruiting, the original plan to enroll 160 patients into each group (normal and obese) was amended to allow enrollment of 220 normal weight patients and 100 obese patients, to be randomized equally into one of four treatment groups, and an additional investigator was added:

Table 16.

Treatment Group	
1	FENTANYL 2-3μg/kg + THIOPENTAL 5-6mg/kg* + ORG 9487 1.5mg/kg
2	ALFENTANIL 20 μg/kg + PROPOFOL 1.5-2 mg/kg + ORG 9487 1.5mg/kg
3	FENTANYL 2-3μg/kg + THIOPENTAL 5-6mg/kg* + SUCCINYLCHOLINE 1.0 mg/kg
4	ALFENTANIL 20 μg/kg + PROPOFOL 1.5-2 mg/kg + SUCCINYLCHOLINE 1.0 mg/kg

*Amended to allow obese patients to be administered 3-6 mg/kg thiopental

[based on Dr. Cortinovis' Table 41, page 71 of his review]

Patients in Groups 1 and 3 initially received 2-3 μg/kg fentanyl over 15 seconds. All patients were preoxygenated for three minutes followed by induction of anesthesia with alfentanil and propofol in Groups 2 and 4, or thiopental in Groups 1 and 3. Patients were randomized to receive either Raplon (1.5 mg/kg) or succinylcholine 1.0 mg/kg IV according to Table 16 above. Immediately following the administration of the anesthetics the line was flushed for 2-3 seconds and then the full dose of muscle relaxant was administered as an IV bolus over 5 seconds. Laryngoscopy was attempted at 50 seconds following the end of the administration of the muscle relaxant. Intubation was to be completed within 60 seconds. If intubation was not possible within 60 seconds, a second attempt was to be made as soon as possible.

The primary efficacy parameter was the percentage of patients with "acceptable" intubation scores, measured as the number of patients who fell into one of four categories: excellent, good, poor or impossible. A blinded assessor evaluated and scored the intubating condition based on the definitions previously described in Table 1. The scores were than collapsed into "acceptable", consisting of excellent and good, or "not-acceptable", consisting of poor and impossible.

Statistical testing was defined as Cochran-Mantel-Haenszel stratified by obesity/normal weight, center and anesthetic technique.

Results:

The following table copied from Dr. Cortinovis' review [p. 78, Table 47], summarizes the patient disposition for this study:

Table 17.

Subject Data Set	Normal Body Weight				Obese				Total
	Org 9487		Succinylcholine		Org 9487		Succinylcholine		
	Fen/thio	Alf/prop	Fen/thio	Alf/prop	Fen/thio	Alf/prop	Fen/thio	Alf/prop	
ASR	59	60	58	57	23	26	27	25	335
AST	58	61	57	58	23	26	28	24	335
ITT	59	60	57	58	23	26	26	26	335
PP	55	58	52	57	21	26	23	24	316

ASR: all subjects randomized

AST: all subjects treated [received drug but had no outcome measurements]

Nineteen subjects were major protocol violators and were not included in the ITT population. In addition, 73 (34 Raplon and 39 succinylcholine) subjects received premedication not permitted by the protocol but deemed necessary by the investigators. The premedications consisted of small doses of sedating agents that the sponsor regarded as having no influence on the outcome of the study.

Treatment groups appeared to be generally matched on relevant measures at baseline.

Primary Efficacy Analyses:

The intubation conditions for the Per Protocol group are summarized in the following table copied from Dr. Cortinovis' Table 51 on page 81 of his review:

Table 18.

	Treatment Group		Difference	2 Sided 95% CI	p-Value
Intubation Condition	Org 9487 N (%)	Succinylcholine N (%)	%	%	
Acceptable	143 (89.4)	152 (97.4)	8.1	(2.0, 14.1)	<0.01
Not Acceptable	17 (10.6)	4 (2.6)			
Excellent	81 (50.6)	114 (73.1)	22.5	(11.4, 33.5)	<0.01
Not Excellent	79 (49.4)	42 (26.8)			

A comparison of the differences between the results in the ITT and the Per Protocol groups are summarized in the following table copied from Dr. Cortinovis' Table 52 on page 81 of his review:

Table 19.

	Acceptable Intubating Conditions		Excellent Intubating Conditions	
	Difference	95% CI	Difference	95% CI
ITT Analysis	7.7%	(1.8%, 13.7%)	22.5%	(11.8%, 33.1%)
PP Analysis	8.1%	(2.0%, 14.1%)	22.5%	(11.4%, 33.5%)

Acceptable intubating conditions were significantly more frequent with succinylcholine than with Raplon, $p < 0.01$. Indeed, acceptable conditions were more often excellent (versus good) with succinylcholine. No significant differences were noted between obese and normal weight patients. Nor were there significant differences between the two anesthetic techniques.

Study 070010:

This was a randomized, parallel group, open-label study performed at three centers in the US and Canada, which compared neuromuscular parameters following either spontaneous recovery or induced reversal from neuromuscular blockade resulting from either 1.5 mg/kg or 2.5 mg/kg of Raplon.

Subjects may have been premedicated with midazolam IV. At the start of preoxygenation (for a maximum of three minutes with 100% O_2) appropriate doses of fentanyl were administered. At the end of preoxygenation anesthesia was induced with propofol IV.

After standardization of the baseline twitch stimulation, a randomized dose of Raplon was administered as per Dr. Cortinovis' Table 67, located on page 97 of his review and reproduced below:

Table 20.

Dose	Reversal
1.5 mg/kg Org 9487 60 subjects	No reversal agent N= 12
	Reversal with 0.05 mg/kg neostigmine at 2 min after Org 9487 administration N=12
	Reversal with 0.07 mg/kg neostigmine at 2 min after Org 9487 administration N=12
	Reversal with 0.05 mg/kg neostigmine at 5 min after Org 9487 administration N=12
	Reversal with 0.07 mg/kg neostigmine at 5 min after Org 9487 administration N=12
2.5 mg/kg Org 9487 60 subjects	No reversal agent N= 12
	Reversal with 0.05 mg/kg neostigmine at 2 min after Org 9487 administration N=12
	Reversal with 0.07 mg/kg neostigmine at 2 min after Org 9487 administration N=12
	Reversal with 0.05 mg/kg neostigmine at 5 min after Org 9487 administration N=12
	Reversal with 0.07 mg/kg neostigmine at 5 min after Org 9487 administration N=12

Sixty seconds following administration of the muscle relaxant the patient may have been intubated. Anesthesia was maintained with nitrous oxide, fentanyl and propofol as clinically indicated. Volatile inhalational agents were not administered until recovery to 80% T4/T1. If subjects recovered to 90% of control T1 or to 80% T4/T1 (whichever time period was longer), an additional dose of a different muscle relaxant was administered.

The primary efficacy parameters were the recovery time to 25% of T1 and recovery index. The former was defined as the time interval from administration of study drug to return of T1 to 25% of control. The latter was defined as the time interval of return of T1 from 25% to 75% of control.

The following secondary efficacy endpoints were recorded and analyzed:

- Recovery time to 50%, 75%, and 90% of T1;
- Recovery time to 70% (80%) T4/T1.

Results:

The following table copied from Dr. Cortinovis' review [p. 102, Table 68], summarizes the patient disposition for this study:

Table 21.

Data Set	Org 9487 1.5 mg/kg					Org 9487 2.5 mg/kg					Total
	No Reverse	Neostigmine @ 2 Min		Neostigmine @ 5 Min		No Reverse	Neostigmine @ 2 Min		Neostigmine @ 5 Min		
		Neostigmine Dose mg/kg					Neostigmine Dose mg/kg				
		.05	.07	.05	.07		.05	.07	.05	.07	
ASR	13	11	12	12	12	12	12	12	11	11	118
AST	13	11	12	12	12	11	12	12	11	11	117
ITT	13	11	12	12	12	11	12	12	11	11	117
PP	11	7	10	12	9	10	12	9	8	9	97

One subject was discontinued prior to administration of study medication and was excluded from the AST.

Twenty subjects were excluded from the Per Protocol analyses because of major protocol violations. These included 11 subjects from the 1.5 mg /kg group and 9 subjects from the 2.5 mg/kg group.

Treatment groups appeared to be generally matched on relevant measures at baseline.

Primary Efficacy Analyses:

The results for Recovery Time to 25% of T1 in the Per Protocol group are summarized in the following table copied from Dr. Cortinovis' Table 73, on page 104 of his review:

Table 22.

Statistical Parameter	Org 9487 1.5 mg/kg					Org 9487 2.5 mg/kg				
	No reversal	Neostigmine @ 2 min		Neostigmine @ 5 min		No reversal	Neostigmine @ 2 min		Neostigmine @ 5 min	
		Neostigmine dose (mg/kg)					Neostigmine dose (mg/kg)			
		0.05	0.07	0.05	0.07		0.05	0.07	0.05	0.07
N	11	7	10	12	9	10	12	9	8	9
Mean	17.3	8.0	7.6	9.1	9.4	24.0	11.7	12.3	12.4	11.7
SD	5.1	1.3	1.3	1.0	1.4	5.0	1.8	2.2	2.7	2.2
Median	17.1	7.6	7.3	9.3	9.2	24.5	11.7	12.3	12.8	11.8
Minimum	10.8	6.2	6.2	7.4	7.5	16.0	9.3	8.9	7.1	7.9
Maximum	25.7	9.9	10.0	10.8	11.8	32.3	14.0	15.3	15.8	14.7

The mean Recovery Times to 25% of T1 for both the 1.5 and 2.5 mg/kg Raplon dose reversal groups were significantly shorter ($p < 0.01$) when compared to the Times for the spontaneous recovery groups.

The Recovery Index scores for the Per Protocol group are summarized in the following table copied from Dr. Cortinovis' Table 74 on page 105 of his review:

Table 23.

Statistical Parameter	Org 9427 1.5 mg/kg					Org 9487 2.5 mg/kg				
	No reversal	Neostigmine @ 2 min		Neostigmine @ 5 min		No reversal	Neostigmine @ 2 min		Neostigmine @ 5 min	
		Neostigmine dose (mg/kg)					Neostigmine dose (mg/kg)			
		0.05	0.07	0.05	0.07		0.05	0.07	0.05	0.07
N	10[a]	7	10	12	9	10	12	9	8	9
Mean	12.1	4.9	7.0	5.3	6.4	14.8	8.6	11.6	8.5	8.0
SD	5.4	1.1	3.9	2.6	2.3	6.0	3.6	4.6	3.1	3.0
Median	12.0	4.5	5.7	5.2	5.8	12.1	7.4	12.5	8.5	7.3
Minimum	4.1	3.6	3.8	2.5	3.3	10.0	3.0	4.2	3.7	5.0
Maximum	21.5	6.7	16.7	12.7	10.7	27.7	15.2	17.2	13.8	15.5

[a] Subject 172 (Org 9487 1.5 mg/kg, no reversal) was reversed prior to completing neuromuscular function measurements (since surgery terminated earlier than anticipated) therefore the time to return of T1 to 75% was not recorded.

The mean Recovery Indices for the 1.5 mg/kg Raplon reversal group were significantly shorter ($p < 0.05$) than those for the spontaneous recovery group. Except for the 2 minute neostigmine 0.07 mg/kg subgroup, the mean Recovery Indices for the 2.5 mg/kg Raplon reversal groups were significantly shorter ($p < 0.05$) when compared with the Indices in the spontaneous recovery group.

Secondary Efficacy Measures:

Within each Raplon dose group, the mean Recovery Times to 50%, 75% and 90% of T1 were shorter for each of the neostigmine reversal groups compared to the corresponding no reversal groups.

Within each Raplon dose group, the mean Recovery Times to 70% and 80% of T4/T1 were significantly shorter ($p < 0.05$) for subjects in each of the neostigmine reversal groups compared to the mean Recovery Times for the no reversal groups. Dr. Cortinovis notes in his review, "The recovery time to 70% and 80% T4/T1 (TOF) ratio is the most clinically useful parameter of the study. These parameters signal that there is satisfactory clinical recovery, that the airway is protected, and ventilatory regulation has recovered adequately." [page 109 of his review] This is the first effective neuromuscular blocking agent which will allow for a relatively rapid recovery from blockade directly from profound block.

Other Studies Supportive of Effectiveness:

Dr. Cortinovis has provided brief reviews of six other studies he believes are supportive of the sponsor's claim for effectiveness. Studies 174305, 070003, 174309, 070002 and 070004 are primarily safety and/or dosing studies for particular subpopulations, although some of these studies do provide additional information regarding the expected time course of neuromuscular blockade as measured by EMG.

Study 070005 is a parallel group, randomized, open-label, multicenter trial comparing the time course of the neuromuscular effects and safety of two Raplon doses, mivacurium, and succinylcholine in adult subjects. This information would appear to provide the only true comparative data assessing time course in the NDA. However, Dr. Cortinovis reports that Raplon had a less favorable time profile than succinylcholine, making it unlikely that the sponsor will attempt to use this study for a comparative claim.

Dr. Cortinovis also performed complete reviews of Studies 174208 and 070006. Study 174208 was an open-label study with a primary endpoint of ease of intubation. I do not believe that this is a viable analysis as the investigator (person performing the intubation) may be easily biased under the circumstances. The secondary efficacy parameters for this study were EMG outcomes. However, the sponsor did not plan, nor did they undertake, any statistical evaluation of the data.

Study 070006 was aborted early due to difficulty with recruitment. The analyses performed in this study were based on a small residual subject population. Therefore, I do not think this study can provide accurate information regarding effectiveness.

Potency:

In Studies 070002 and 070004, the sponsor evaluated potency in order to make dosing recommendations for the pediatric and geriatric patient populations. The ED_{50} was estimated for each group based on EMG measurements. In his review, Dr. Permutt describes the analyses used to make these estimates [pages 10-13]. He concludes that the estimated ED_{50}'s are reasonably informative, even if subject to wide uncertainty. These estimates are: 0.3 mg/kg for neonates less than 1 month old and infants from 1 month to less than 1 year; 0.4 mg/kg for patients 1 to 12 years; and, 0.3 mg/kg for adult and geriatric patients, 18 years and over.

SAFETY:

A total of 1973 patients received Raplon in the sponsor's clinical program, including 929 subjects in the US studies and 1044 in the non-US studies. Most subjects received a single dose of Raplon. Doses administered to those subjects are summarized in Dr. Cortinovis' Table 88, page 122 of his review. Seventy-three subjects in the US studies were treated with a single 5 second bolus injection (1.5 mg/kg) for intubation and an initial maintenance infusion of 3 mg/kg/hr for periods ranging from 45 to 60 minutes. In non-US studies, 30 subjects received a Raplon infusion following the initial intubating dose of 1.5 mg/kg. In three non-US studies, Raplon was administered to 100 subjects by repeated bolus maintenance dosing.

Deaths:

Nine patients died in the US studies. Only two of these were treated with Raplon. The first of these two patients was a 43 year old sickle cell patient who developed an intracerebral hemorrhage and died, over three and a half months after treatment with Raplon followed by an uneventful choledochoduodenosotomy

The second patient was a 71 year old man who developed acute onset of moderately severe hypotension (75/45 at 5 minutes vs. 138/750 at study drug administration) after treatment with Raplon 3.0 mg/kg during induction for a right upper lobectomy for cancer. The hypotension reportedly responded to treatment with phenylephrine. However, the patient developed sinus tachycardia 12 hours after surgery. This adverse event occurred after he had received a blood transfusion. His creatine kinase increased from 89 pre-operatively to 2542 on the first postoperative day. The patient expired three days postoperatively having developed respiratory, renal and right ventricular failure. While the episode of hypotension may well have been directly due to the administration of Raplon, the patient's death was due to multiorgan failure, not directly, and possibly not indirectly, related to the hypotensive event.

One patient in the non-US study population died and this death was reported in the 120 Day Safety Update. This patient had received a single dose of Raplon before undergoing a craniotomy to evacuate a trauma induced hematoma. Cerebral edema worsened six days after the surgery and the patient expired following a cardiac arrest and uncal and tonsillar herniation on the seventh post-operative day.

Discontinuations:

There were no discontinuations due to adverse events.

Serious Adverse Events:

Dr. Cortinovis has included in his review (pages 125-129) a copy of the sponsor's summary table of serious adverse events [SAE's]. Review of this table documents few

SAE's attributable to study drug per the investigators. Of these five events, bronchospasm occurs in two patients along with tachycardia in one of the patients, hypotension occurs in a third patient, and hemiparesis occurs in a fourth patient. Each of the four patients recovered from the SAE.

In the 120 Day Safety Update, the sponsor reports on a patient with traumatic head injury in Study 174304 (evaluating the effects of Raplon on intracranial pressure) who developed a marked elevation of his ICP two minutes after administration of Raplon 120 mg IV. He was treated with hyperventilation and an increase in his dopamine infusion rate. The elevation lasted for five minutes. This patient had had a similar episode of transiently increased ICP earlier the same day.

Other Adverse Events:

The most common adverse events in the adult and geriatric patients treated Raplon were hypotension (6.1%), bronchospasm (4%), and tachycardia (2.5%). In pediatric patients the most common adverse events were: hypotension (5.1%), prolonged anesthetic emergence (5.1%), and unplanned endotracheal extubation (2.6%). Erythematous rash occurred in 2.6% of the infant patients.

Dr.Cortinovis has expressed concern regarding the effect of Raplon on the newborns exposed via their mothers in Study 070006. This study compared the effects of Raplon and succinylcholine for rapid sequence intubation in women undergoing cesarean section under general anesthesia. On page 136 of his review, Dr. Cortinovis states, "APGAR scores of 6 or less were given to 4 newborns at one minute in both groups. By 5 minutes, all but one in each group had scores greater than 6." He also notes that the Raplon exposed newborns had consistently higher umbilical artery and venous pCO_2 levels and consistently lower pO_2 levels than the succinylcholine exposed neonates. Finally, he reports on a single newborn exposed to Raplon who had a high umbilical/maternal drug concentration and who developed respiratory distress system at delivery, recovering after 12 hours. This patient was born with an imperforate anus.

With equal numbers of low APGAR scores found in both the Raplon and comparator exposed neonates, no conclusion may be drawn regarding the role of the study drug in this adverse event. While review of the mean and median umbilical artery and venous pCO_2 and pO_2 levels [Table 96, p. 137 of Dr. Cortinovis' review] does confirm the results as noted by Dr. Cortinovis, no statistical analysis has been performed on these relatively close numbers, and no analysis has been undertaken to assess differences in the maternal populations. While the single patient discussed does raise the possibility of a drug related serious adverse event, in isolation it is difficult at best to directly or indirectly correlate the SAE with drug exposure, especially in light of the patient's medical condition. Thus, I do not think it is possible to draw any significant conclusion regarding the possibility of a negative impact of Raplon on neonates whose mothers have been treated with the drug during cesarean section.

Finally, Dr. Cortinovis has pointed out in his conclusions, that in the report for Study 174302 the sponsor describes a single patient who had been treated with Raplon infusion and whose T4/T1 ratio dropped to 0.64 within 10 minutes of the ratio having spontaneously recovered to 0.7. This degradation of neuromuscular function after attaining evidence of adequate spontaneous recovery from blockade represents an event generally considered to be great clinical concern.

Laboratory Values:

Post-surgical laboratory data was only collected in the adult patients from five of the US studies. Dr. Cortinovis has noted an apparent dose related increase in creatine kinase [CK] levels in the Raplon treated subjects compared to the placebo group. He was unable to locate follow-up results for these patients, but no early or late clinical reports associated with these CK elevations were submitted to the NDA. In response to a request for explanation of these findings, the sponsor reported that 76% of the cases of elevated CK occurred in Study 070011 and that the subjects in this study were in general older and sicker than the subjects in the overall development program. These subjects were also undergoing surgical procedures involving more muscle trauma and lung involvement, and requiring more blood draws. Dr. Cortinovis requested further analyses of these data and the sponsor's response to that request is under review at this time.

While the apparent dose related CK elevations in the Raplon treated patients does raise some concern, the comparison Dr. Cortinovis has evaluated looks at drug treated patients from across a number of studies versus placebo patients reportedly from only one of these studies. The sponsor's explanation for these results is logical and sound, but will require further review. In addition, the absence of associated clinical adverse events occurring during the CK elevations or further out post-operatively, even in the absence of follow-up laboratory results, brings into question the clinical significance of these findings. [Further analysis by Dr. Permutt documents that the dose effect is due to the large percentage of high dose treated patients in the 070011 study, and is not an internal dose effect within that study.]

Plasma histamine levels were assessed in Study 070011. Clinically significant levels were found to be dose related with 6%, 13% and 40% of subjects in the 1.0, 2.0 and 3.0 mg/kg groups demonstrating elevations.

Vital Signs and ECG:

No clinically significant changes occurred in the Raplon studies other than those already discussed above.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS:

Dr. Doddapaneni reports, in his review, on a mass balance study which documented that the mean combined excretion in urine and feces after continuous collection for 13 and ½ days was approximately 56%. Measurable concentrations of radiocarbon were then detected in urine collected once a week for four more weeks. The sites of drug deposition and the length of time to complete excretion in humans are not known. It remains unclear whether some drug may remain in the body indefinitely.

PRECLINICAL PHARMACOLOGY AND TOXICOLOGY:

A review, by Dr. Jean, of the available animal data from previously approved drugs in this class has not provided evidence of a similarly long elimination profile to rapacuronium. In light of the documented target organ uptake for rapacuronium in the animal studies, which includes the heart, liver, kidneys, bone, muscle and pituitary gland, concerns regarding chronic exposure are significant, especially in the pediatric population. While some of these exposures may be in amounts which comprise only a small percentage of the total drug load, the chronicity of the exposure remains unknown.

In addition, preclinical toxicology studies revealed dose and duration related adverse ECG changes in dogs and cats. These changes included prolongation of the QT interval in the dogs at doses which may be used clinically when the drug is administered as high dose boluses or as a prolonged infusion.

COMMENTS:

The sponsor has submitted two adequate and well-controlled studies documenting the effectiveness of Raplon as a neuromuscular blocker when used for intubation prior to elective surgery. The sponsor initially attempted to document equivalency of this endpoint (ease of intubation) between Raplon and succinylcholine, but the results were not supportive and no equivalency claims may be made.

In addition to the primary efficacy measurement of ease of intubation, the sponsor has submitted a number of studies which provide support for certain advantages for their product in regard to the time course of neuromuscular blockade. While this data is primarily descriptive, both Drs. Cortinovis and Permutt have concluded that there is an adequate amount of well defined data to appropriately label the product as having a rapid onset and a short duration of action. However, the duration of action does appear to be dose dependent (intermediate duration at 2.5 mg/kg) and careful delineation of this finding will be necessary when describing the time course of action. The most important and unique finding in the time course evaluations is that the neuromuscular blocking activity of Raplon can be reversed from a deep level of blockade.

Dr. Cortinovis has raised a number of safety concerns regarding this product. While I think that the available data regarding neonatal toxicity due to exposure during cesarean section is not compelling, the matter of prolonged elimination kinetics and the target organ uptake pattern for Raplon raise clear-cut safety concerns, especially in the pediatric population. The preclinical findings of cardiotoxicity at high doses of this product add another dimension to this matter of prolonged elimination, particularly in the face of repeated dosing or continuous infusion. Until further information is available regarding the elimination pattern for Raplon in adults, after single and repeated administration, I do not think further exposure in the pediatric population is acceptable.

At this time, the data regarding elevated creatine kinase levels does not appear to be based on a drug induced effect and no clinical adverse events appeared to correlated with the elevations. However, this finding does bring into question the possibility of muscle or neuromuscular junction damage with prolonged exposure to rapacuronium and other drugs of this class. Long term safety studies may be useful to provide further information regarding this possibility.

Finally, the single reported case of degradation of neuromuscular function after attaining an adequate recovery profile following treatment with Raplon remains of concern. However, the patient recovered to baseline and no clinically significant, associated adverse events were reported. Carefully monitoring of post-marketing safety data will, hopefully, provide early warning for this particularly troublesome problem, if it is rapacuronium related.

RECOMMENDATIONS:

I recommend that the NDA be approved with appropriate labeling.

Bob A. Rappaport, M.D.

April 5, 1999

Organon

ORGANON Inc.

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PATENT INFORMATION AND ORIGINAL DECLARATION

PATENT INFORMATION

21 CFR 314.53(c)(1)

(I) U.S. Patent No. 5,418,226

Expiration Date - April 14, 2013

(ii) Type of Patent - Drug Product

(iii) Name of Patent Owner of Record

Akzo N.V.
Arnhem, Netherlands

(iv) Name of Attorney

William M. Blackstone, Esq.
Akzo Nobel
1300 Piccard Drive
Suite 206
Rockville, MD 20850-4396

ORIGINAL DECLARATION

21 CFR 314.53(c)(2)

The undersigned declares that Patent No. 5,418,226 covers the formulation, composition and/or method of use of ORG 9487 for Injection. This product is the subject of the application for which approval is being sought.

Patrick J. Osinski
Vice President and Secretary
Organon Inc.

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rev0498

EXCLUSIVITY SUMMARY FOR NDA # _20-984_____ SUPPL #_____

Trade Name _RAPLON_____Generic Name _rapacuronium bromide_____

Applicant Name Organon, Inc._____ HFD # 170_____

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /_X_/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X_/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?
5 Years

e) Has pediatric exclusivity been granted for this Active Moiety?

_No_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X_/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # YES /__/ ! NO /___/ Explain: _____

!

! _____

Investigation #2 !

!

IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

!

YES /___/ Explain _____ ! NO /___/ Explain _____

!

_____ ! _____

!

_____ ! _____

!

!

Investigation #2 !

!

YES /___/ Explain _____ ! NO /___/ Explain _____

!

_____ ! _____

!

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____ 4/12/99

Signature Date

Title: Regulatory Project Manager

_____ 4/12/99

Signature of Office/ Date
Division Director

8/17/99

cc: Original NDA Division File HFD-93 Mary Ann Holovac

Organon

ORGANON Inc.

CONFIDENTIAL

CERTIFICATION

Pursuant to Section 306 (k) (1) of the Federal Food, Drug and Cosmetic Act, the undersigned certifies that Organon Inc. did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [Section 306 (a) or (b)], in connection with the New Drug Application for Org 9487 (rapacuronium bromide) for Injection, NDA No. 20-984.

Albert P. Mayo
Director, Regulatory Affairs

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA # 20-984_____ Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-170_____ Trade and generic names/dosage form:Raplon (rapacuronium bromide) for injection, 100 and ~~mg/mL~~, 200 mg~~/10 mL~~ Vials

Action: AP

Applicant Organon, Inc._____ Therapeutic Class 1S_____

Indication(s) previously approved NA_____
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate X

Indication in this application Indicated for outpatients and inpatients as an adjunct to general anesthesia to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgical procedures

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

_X_ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). **See comments below:**

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

- ___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- ___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- ___ c. The applicant has committed to doing such studies as will be required.
  - ___ (1) Studies are ongoing,
  - ___ (2) Protocols were submitted and approved.
  - ___ (3) Protocols were submitted and are under review.
  - ___ (4) If no protocol has been submitted, attach memo describing status of discussions.
- ___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply, attach an explanation, as necessary.**

Comments:

Needs more exposure in newborn period 0-1 month.

Before further pediatric exposure is contemplated, particularly multiple dose, preclinical studies to evaluate effect of sequestration in tissues and developing organs should be conducted.

The safety of long-term exposure in adults (multiple dose and infusion as in the ICU setting) should be established first.

Signature of Preparer and Title

08-02-99
Date

Director Concurrence

8-2-1999
Date

cc: Orig NDA #20-984
HFD-170/Div File
NDA/PLA Action Package
HFD-006/ SOImstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 8/2/99)

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA # 20-984_____ Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-170_____ Trade and generic names/dosage form:Raplon (rapacuronium bromide) for injection, ~~100 mg/mL, 200 mg/10 mL~~_____

Action: ~~AR~~ AE

Applicant Organon, Inc._____ Therapeutic Class 1S_____

Indication(s) previously approved NA_____
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate X__

Indication in this application Indicated for outpatients and inpatients as an adjunct to general anesthesia to facilitate tracheal intubation, and to provide skeletal muscle relaxation during surgical procedures

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  - ___ (1) Studies are ongoing,
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  - ___ (3) Protocols were submitted and are under review.
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Comments:

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The safety of long-term exposure in adults (multiple dose and infusion as in the ICU setting) should be established first.

(Regulatory Project manager)
Signature of Preparer and Title

4/12/99
Date

Concur.

4/12/99

cc: Orig NDA/PLA/PMA #_____
HF_____/Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 4/12/99)