

Table 83 Percent Twitch Depression: Per-Protocol Group

Parameter	Dose Group		
	0.3 mg/kg	0.6 mg/kg	0.9 mg/kg
Subject Group: Non-Geriatric (N=29)			
N	9	9	11
Mean ± SD	42±25	93±9	100±1
Median	46	100	100
Min-Max	0-74	74-100	97-100
Subject Group: Geriatric (N=11)			
N	4	3	4
Mean ± SD	57±36	93±7	94±11
Median	51	93	100
Min-Max	27-100	85-100	78-100
All (N=40)			
N	13	12	15
Mean ± SD	47±28	93±8	98±6
Median	46	96	100
Min-Max	0-100	74-100	78-100

Sponsor's Table 12 Vol 82, p.0061

- Onset Time: (Defined as the time interval, in seconds, between the time of Org 9487 was administered and the peak effect.)

Table 84 Onset Time: Per Protocol Group

Parameter	Dose Group		
	0.3 mg/kg	0.6 mg/kg	0.9 mg/kg
Subject Group: Non-Geriatric (N=28)			
N	8	9	11
Mean ± SD	148±47	97±32	83±19
Median	145	90	80
Min-Max	60-222	58-140	50±120
Subject Group: Geriatric (N=11)			
N	4	3	4
Mean ± SD	173±36	183±76	137±44
Median	186	150	123
Min-Max	120-200	130-270	100-200
All (N=39)			
N	12	12	15
Mean ± SD	156±44	118±57	97±36
Median	160	120	90
Min-Max	60-222	58-270	50-200

Sponsor's Table 13 Vol 82 p.0063

Increasing the dose of Org 9487 resulted in shorter onset times, a property reported with other nondepolarizing relaxants. Sponsor quotes FDA's definition (as delineated by Bedford) of "rapid onset" as onset occurring in 1-2 minutes. Sponsor states the onset times were rapid in the non-geriatric 0.6mg/kg and 0.9 mg/kg dose groups as well as in the geriatric 0.9 mg/kg dose group.

This reviewer does not agree that the 0.9mg/kg dose in the geriatric population met the Bedford definition of "rapid onset". This group had a Mean onset time of 137 sec and a Median onset time of 123 sec; these values are more than the 2-minute upper interval that defines "rapid onset".

### SECTION 9.9.1.7 STUDY 174302

TITLE: Maintenance of Neuromuscular Block with Org 9487 or Rocuronium Following an Intubating Dose of Org 9487.

This was an open label, parallel group, comparative, randomized, multicenter study involving 90 subjects divided into 6 groups. The primary objective was to compare the spontaneous and neostigmine assisted recovery from 25% of initial control T1 after maintenance of neuromuscular block for 30 min with either Org 9487 or rocuronium following an intubating dose of Org 9487. Subjects were adults (>18 ≤65 years) scheduled for elective surgery.

Subjects were divided into 6 groups:

Table 85 Study Flow

GROUP 1	GROUP 2	GROUP 3	GROUP 4	GROUP 5	GROUP 6
Org 9487 Bolus	Org 9487 Bolus	Org 9487 Infusion	Org 9487 Infusion	Rocuronium Bolus	Rocuronium Bolus
N= 14 All subjects treated	N=16 All subjects treated	N=15 All subjects treated	N=15 All subjects treated	N=15 All subjects treated	N=15 All subjects treated
Intubation: Org 9487 1.5mg/kg	Intubation: Org 9487 1.5mg/kg	Intubation: Org 9487 1.5mg/kg	Intubation: Org 9487 1.5mg/kg	Intubation: Org 9487 1.5mg/kg	Intubation: Org 9487 1.5mg/kg
Org 9487 Bolus 0.5 mg/kg x 3 Given when T1 25% of Control	Org 9487 Bolus 0.5 mg/kg x 3 Given when T1 25% of Control	Org 9487 4mg/kg/hr Given when T1 @ 5-10% control to maintain block of 80-100% Infusion continued x 30 minutes	Org 9487 4mg/kg/hr Given when T1 @ 5-10% control to maintain block of 80-100% Infusion continued x 30 minutes	Rocuronium Bolus 0.15 mg/kg x 2 Given when T1 25% of Control	Rocuronium Bolus 0.15 mg/kg x 2 Given when T1 25% of Control
Reversal: None	Reversal: Neostigmine 0.05 mg/kg given at recovery T1 25% Control after 3 <sup>rd</sup> bolus	Reversal: None	Reversal: Neostigmine 0.05 mg/kg given at recovery T1 25% Control after end of infusion	Reversal: None	Reversal: Neostigmine 0.05 mg/kg given at recovery T1 25% Control after 2nd bolus

Efficacy analysis demonstrated the following:

- The median infusion rate of Org 9487 necessary to maintain a neuromuscular block 80-100% was 3.25 (1.69-3.68) mg/kg/hr in Group 3 and 2.47 (1.08-4.58) mg/kg/hr in Group 4.
- No difference in times (25%-75%; 25%-0.7 T4/T1; 25%-0.8 T4/T1) were noted for spontaneous recovery after 3 maintenance doses of Org 9487 vs an infusion of Org 9487.
- The recovery times utilizing neostigmine were statistically significantly longer (25%-0.7 T4/T1) after 3 maintenance doses of Org 9487 as compared to an infusion of Org 9487 for 30 minutes.
- Comparison of recovery after neostigmine between bolus Org 9487 and bolus rocuronium: no statistical difference in rate of recovery in the 25%-75% parameter but Org 9487 was statistically significantly longer than the rocuronium in the recovery measurements of 25%-0.7 T4/T1 and 25%-0.8 T4/T1.
- Administration of neostigmine at T1 to 25% of control statistically significantly reduced all recovery times after all treatments.
- A cumulative effect was observed with the three maintenance (bolus) doses of Org 9487: the duration of T1 to 25% of control was statistically significantly increased with increasing number of doses. The duration of T1 to 25% of control of the second and third maintenance dose of Org 9487 was statistically significantly longer than the duration of T1 to 25% of control of the first and second maintenance dose of Org 9487.
- One Group 3 subject had recovery to 0.7 T4/T1 drop within 10 minutes to 0.64 T4/T1.

**Reviewer Discussion:**

The increase in recovery times after each succeeding bolus dose of Org 9487 given for maintenance is noteworthy. Sponsor agrees the spontaneous recovery times after 3 maintenance doses of Org 9487 and after an infusion of Org 9487 for 30 minutes were statistically significantly longer than after 2 maintenance doses of rocuronium. According to sponsor, the differences between treatment groups in spontaneous recovery data might be explained by the formation and action of the 3-desacetyl metabolite of Org 9487, Org 9488. Sponsor quotes literature references that suggest Org 9488 might be responsible for the longer neuromuscular recovery of Org 9487 after prolonged administration.

Also of concern is the one Org 9487 patient given an infusion dose who developed degradation of neuromuscular function after attaining evidence of adequate neuromuscular activity. This individual reached a T4/T4 recovery of 0.7 and, within 10

minutes regressed to a T4/T1 of 0.64. T4/T1 0.7 is generally accepted as adequate clinical recovery.

## SECTION 10.0 SAFETY ANALYSIS

### SECTION 10.1 EXPOSURE

The clinical and laboratory safety of Org 9487 has been evaluated through clinical investigation conducted by Organon Inc in the U.S. and Canada (under IND No. ) and Organon Teknika in Europe. Comprising the Integrated Summary of Safety are 13 US studies and 24 Non-US studies. The studies contain 1263 subjects in the US studies and 1533 subjects in Non-US studies. The subset of subjects exposed to Org 9487 includes 929 subjects in US studies and 1044 subjects in Non-US studies. Remaining subjects received either placebo, Org 9488 (3-OH metabolite of Org 9487) or an active control (succinylcholine, mivacurium, rocuronium, or vecuronium). The 120 Day Safety Update added another 66 patients to the safety data base, 63 of whom received Org 9487.

Table 86 ENUMERATION OF SUBJECTS/PATIENTS

STUDY GROUP	Treatment Groups			
	Org 9487	Active Control	Placebo	Org 9488
Completed Phase 1				
Single Dose	74	15		
Multiple Dose	6			
Phase I SubTotal	80	15	0	
Completed Phase 2-3				
Single Dose	1533	654	81	14
Multiple Dose	196	51	0	0
Phase II SubTotal	1729	705	81	14
Ongoing Phase 2,3 Studies				
Single Dose	59	5	3	0
Multiple Dose	105	0	0	0
Phase III SubTotal	164	5	3	0
GRAND TOTAL	1973	725	84	147

## SECTION 10.2 DEMOGRAPHICS

The following is a summary of demographic and physical characteristics of treated subjects:

Table 87 U.S. and Non-U.S. Phase 1, 2, and 3 Studies: All-Subjects-Treated Group  
Cut Off Date October 10, 1997

DEMOGRAPHICS	Org 9487 N=1967	Active Control N=725	Placebo N=84	Org 9488 N=14
AGE N (%)				
Neonates (< 1 month)	39(2)	0	0	0
Infants (1 month to < 2 yr)	168(9)	0	0	0
Children (2yr to ≤ 12 yr)	177(9)	23(3)	0	0
Adults (18 to < 65)	1374(70)	609(84)	060(71)	14(100)
Geriatric (≥ 65)	209(11)	93(13)	24(29)	0
SEX Neonates N (%)				
Male	30(77)	0	0	0
Female	9(23)	0	0	0
SEX Infants N (%)				
Male	132(79)	0	0	0
Female	36(21)	0	0	0
SEX Children N (%)				
Male	114(64)	6(26)	0	0
Female	63(36)	17(74)	0	0
SEX Adults N (%)				
Male	689(50)	331(54)	29(48)	11(79)
Female	685(50)	278(46)	31(52)	3(21)
SEX Geriatric N (%)				
Male	114(55)	51(55)	13(54)	0
Female	95(45)	42(45)	11(46)	0
RACE Neonates N (%)				
Caucasian	29(74)	0	0	0
Non-Caucasian	10(26)	0	0	0
RACE Infants N (%)				
Caucasian	0	0	0	
Non-Caucasian	0	0	0	
RACE Children N (%)				
Caucasian	138(79)	11(48)	0	0
Non-Caucasian	39(22)	12(52)	0	0
RACE Adults N (%)				
Caucasian	1027(85)	448(89)	49(82)	14(100)
Non-Caucasian	177(15)	55(11)	11(18)	0
RACE Geriatrics N (%)				
Caucasian	161(88)	64(93)	20(83)	0

DEMOGRAPHICS	Org 9487 N=1967	Active Control N=725	Placebo N=84	Org 9488 N=14
Non-Caucasian	22(12)	5(7)	4(17)	0
HEIGHT Neonates (cm)				
Mean ± SD	52±3			
Median	52			
HEIGHT Infants (cm)				
Mean ± SD	69±10			
Median	69			
HEIGHT Children (cm)				
Mean ± SD	119±23	107±23		
Median	119.5	111		
HEIGHT Adults (cm)				
Mean ± SD	170±10	171 ± 11	169 ± 10	180 ± 9
Median	170	171	168.5	
HEIGHT Geriatrics (cm)				
Mean ± SD	169±10	167 ± 9	170 ± 10	
Median	168	167.5	168	
WEIGHT Neonates (kg)				
Mean ± SD	3±0			
Median	3.5			
WEIGHT Infants (kg)				
Mean ± SD	8±2			
Median	8.5			
WEIGHT Children (kg)				
Mean ± SD	24±11	19±6		
Median	22	19.3		
WEIGHT Adults (kg)				
Mean ± SD	73±15	76±15	73±14	82±11
Median	72	75	71.1	79.75
WEIGHT Geriatrics (kg)				
Mean ± SD	73±15	70±13	75±15	
Median	72	70	77	
ASA CLASS N (%)				
Neonates + Infants + Children				
ASA 1	295(77)	17(74)	0	0
ASA 2	87(23)	5(22)	0	0
ASA 3	2(1)	1(4)	0	0
ASA 4	0	0	0	0
ASA 5	0	0	0	0

DEMOGRAPHICS	Org 9487	Active Control	Placebo	Org 9488
	N=1967	N=725	N=84	N=14
ASA CLASS				
Adults + Geriatrics N (%)				
ASA 1	827(54)	384(56)	18(21)	10(71)
ASA 2	550(36)	247(36)	31(37)	4(29)
ASA 3	149(10)	42(6)	22(26)	0
ASA 4	12(1)	14(2)	13(15)	0
ASA 5	0	0	0	0

Table Prepared by Sponsor February 10, 1999 at Request of Reviewing Medical Officer

NOTE: 6 C-14 Org 9487 treated subjects from study 174104 are not included.  
Race was not recorded for 170 adult Org 9487 treated subjects and 106 adult Active Control treated subjects and for 26 geriatric 9487 treated subjects and 24 geriatric Active Control treated subjects.  
ASA Clas was not recorded for one adult Org 9487 treated subject.  
Height was not recorded for 3 neonates, 20 infants, and 11 Org 9487 treated and 6 mivacurium treated children; 18 Org 9487 treated and 7 Active Control treated adults; and 6 Org 9487 treated and 1 Active Control treated geriatric subject.  
Weight was not recorded for 1 infant.

### SECTION 10.3 DOSING

Most of the subjects in this application received a single dose of Org 9487. There were also subjects who received either an infusion of Org 9487 or multiple bolus injections of study drug. Data on subjects who received only a single dose of Org 9487 is contained in Table 88.

Table 88: Single Dose Exposure Us And Non-Us Studies (Cutoff Date October 10,1997)

Age Group	Org 9487 mg/kg				Total
	< 1.35	1.35-1.65	1.7-2.75	> 2.75	
Adults	122	954	185	38	1299
Geriatrics	37	136	30	6	209
Neonates	30	5	4	0	39
Infants	75	15	53	25	168
Children	56	20	62	39	177
Total	320	1130	334	108	1892

Data derived from Sponsor's Table 33 (US Studies and Table 36 Non-US Studies)  
Vol 153 ISS

For dosing by infusion, in the US Studies Org 9487 was administered to 73 subjects as a single 5 second bolus injection (1.5 mg/kg) for intubation and an initial infusion rate of 3 mg/kg/hr for maintenance of muscle relaxation from a minimus of 45 minutes to a maximum of 60 minutes. The mean infusion amount was 2.1 mg/kg with a range of 0.8-5.6 mg/kg. In the Non-US studies, following an intubating dose of 1.5mg/kg of Org 9487,

30 subjects received an infusion of Org 9487 for about 30 minutes. In three Non-US studies, Org 9487 was administered to 100 subjects by repeated bolus maintenance dosing.

## SECTION 10.4 DEATHS

As of the Cutoff Date of October 10, 1997, no subjects died in the Non-US Studies. Table 89 is a listing of subjects who died in US Phase 2 and 3 Studies.

Table 89: Listing of Subjects who Died US Phase 2 and 3 Studies, All Subjects Treated Group (Cutoff Date October 10, 1997)

Treatment	Age	Gender	Dose Mg/kg	Day of Event	Event
Org 9487	43	M	2.5	115	Resp Failure
Org 9487	71	F	3.0	115	Intracerebral Hemorrhage
				1	Resp failure
				1	Sinus Tachy
				1	R. Vent failure
				1	Pulmonary Edema
				2	Renal Failure
Placebo	77	F	0	5	Cardio-Resp arrest
Active Control	91	F	0.6 Rocuronium	2	L. Sided Hemiparesis

Modified Sponsor's Table 47, Vol 153, ISS p. 0169

There were two deaths among the subjects who received Org 9487:

Subject 220 (Study 070005):

43 year old with sickle cell disease received Org 9487 and underwent an uneventful choledochoduodenostomy. Over three and a half months later he was readmitted due to an intracerebral hemorrhage and expired.

Subject 116 (Study 070011):

71 year old underwent a right upper lobectomy for cancer after receiving fentanyl/etomidate for induction of anesthesia. Org 9487 3.0mg/kg was administered. Blood Pressure prior to Org 9487 was 138/75. Within 5 minutes after administration of Org 9487 the blood pressure had dropped to 75/45. The hypotension was treated with IV phenylephrine. The patient developed sinus tachycardia 12 hours after surgery after receiving a blood transfusion. The Creatine Kinase increased from 89 pre-operatively to 2542 on the first postoperative day. The urine output was marginal to very low following surgery. Over a period of 22 hours the patient's respiratory status declined. Three days postoperatively the patient expired after experiencing respiratory failure, renal failure, and right ventricular failure.

**SECTION 10.5 DISCONTINUATIONS**

No subjects in the Org 9487 Clinical Development program (US and Non-US) discontinued due to an Adverse Event.

**SECTION 10.6 SERIOUS ADVERSE EVENTS**

Table 90 is a listing of subjects with serious adverse events from the US and Non-US Phase 2 and 3 studies. In addition to the Org 9487 exposed subjects, the table presents details on SAEs for Org 9488, rocuronium, mivacurium and succinylcholine.

Table 90: Listing of Subjects with Serious Adverse Experiences: U.S. and Non U.S. Phase 2 and 3 Studies: All-Subjects Treated Group  
(Cutoff Date = October 10, 1997)

Study/Subject	Gender/Age	Dose Mg/kg	Day	Time	System Organ Class	Preferred Term	Investigator Term	Action Taken	Outcome	Study Drug Relation by Investigator
Org 9487										
070001/										
128	M/29Y	2.0	0	0:01	Heart Rate and rhythm disorders	Tachycardia	Tachycardia	None	Recovered	Definite
			0	0:01	Respiratory System Disorder	Bronchospasm	Bronchospasm	None	Recovered	Definite
238	F/78Y	1.0	0	6:27	Urinary System Disorders	Oliguria	Oliguria	None	Recovered	Unlikely
301	M/60Y	1.0	0	2:21	GI System Disorder	Vomiting	Vomiting	None	Recovered	None
			0	2:21	Urinary System Disorder	Urinary Retention	Urinary Retention	None	Recovered	None
			0	2:21	GI system disorder	Nausea	Nausea	None	Recovered	None
358	F/49Y	1.0	0	2:34	Platelet, Bleeding & Clotting Disorders	Haemoperitoneum	Haemoperitoneum	None	Recovered	None
513	F/63Y	2.5	0	3:06	Myo Endo Pericardial & Valve disorders	Myocardial Infarction	Myocardial Infarction And ischemia	None	Still present	None
070002/										
134	M/3mo	0.9	42	NA	Cardiovascular disorders, General	Cardio-Respiratory Arrest	Cardio-respiratory Arrest	None	Recovered	None
224	M/11 mo	0.6	0	4:49	Secondary Terms	Postoperative bleeding	Cleft Palate Post Op Bleed	None	Recovered	None
070003/										
153	F/42 Y	1.5	7	N	Platelet, bleeding & clotting Disorders	Thrombosis	Thrombosed Catheter	None	Recovered	None
155	F/20Y	1.5	14	NA	Platelet, bleeding & clotting Disorders	Thrombosis	Permacath clotted	None	Recovered	None
070004/										
101	F/28Y	0.6	0	UNK	GI System disorders	Abdominal pain	Abdominal pain	None	Recovered	None
			0	UNK	Urinary system disorders	Urinary retention	Inability to urinate	None	Recovered	None
120	F/37Y	0.9	3	NA	Reproductive disorders, female	Plevic inflammation	Pelvic inflammatory Disease	None	Recovered	None
			3	NA	Liver and biliary system disorders	Cholelithiasis	Cholelithiasis	None	Recovered	None
152	F/74Y	0.6	0	2:14	Secondary terms	Surgical complication	Transection of Inferior vena cava	None	Recovered	None

Study/ Subject	Gender/ Age	Dose Mg/kg	Day	Time	System Organ Class	Preferred Term	Investigator Term	Action Taken	Outcome	Study Drug Relation by Investigator
070005/ 220	M/43Y	2.5	115	NA	Respiratory system disorder	Respiratory insufficiency	Respiratory failure	None	Died	None
			115	NA	Vascular (extracardiac) disorders	Cerebral hemorrhage	Intracerebral Hemorrhage	None	Died	None
313	F/48Y	1.5	3	NA	GI system disorders	Ileus	Ileus	None	Recovered	None
070007/ 527	F/29Y	1.5	0	4:57	GI system disorders	Nausea	Post Op nausea	None	Recovered	Unlikely
			0	4:57	GI system disorders	Vomiting	Vomiting	None	Recovered	Unlikely
531	F/53Y	1.5	0	2:07	Reproductive disorders, female	Vaginal bleeding	Excessive vaginal Bleeding	None	Recovered	unlikely
572	M/66Y	1.5	0	0:00	Cardiovascular disorders general	Hypotension	Hypotension	None	Recovered	Possible
578	F/69Y	1.5	0	0:04	Platelet bleeding & clotting Disorders	Epistaxis	Nasal epistaxis	None	Recovered	Unlikely
			8	N	GI system disorders	GI disorder NOS	Colocutaneous fistula, Ischemic L. leg	None	Recovered	None
583	M/73Y	1.5	0	UNK	GI system disorders	Hemorrhage rectum	Rectal tear	None	Recovered	None
070008/ 108	M/20days	1.0	0	2:16	Respiratory system disorders	Respiratory Insufficiency	Respiratory insufficiency	None	Recovered	None
070009/ 108	M/66Y	1.5	1	NA	Centr & Periph nervous system Disorders	Hemiparesis	CVA and related Deficits	None	Still Present	Unlikely
116	F/74Y	1.5	0	UNK	Centr & Periph nervous system Disorders	Hemiparesis	Probable Lt sided Cereb vasc Accident ?	None	Still Present	None
070010/ 161	F/47Y	1.5	2	NA	Urinary system disorders	Urinary tract infection	Urinary tract infection	None	Still Present (Recovered in final study report)	None
		1.5	2	NA	GI system disorders	Ileus	Ileus	None	Still Present (Recovered in final study report)	None

Study/ Subject	Gender/ Age	Dose Mg/kg	Day	Time	System Organ Class	Preferred Term	Investigator Term	Action Taken	Outcome	Study Drug Relation by Investigator
		1.5	2	NA	Body as a whole- General disorders	Fever	Elevated temp	None	Still Present (Recovered in final study report)	None
070011/ 106	M/75Y	3.0	0	11:37	Heart rate and rhythm disorders	Arrhythmia atrial	Arrhythmias	None	Still present	None
			6	NA	Respiratory system disorders	Dyspnea	Respiratory distress	None	Still present	None
			3	NA	Red blood cell disorders	Anemia	Low hematocrit	None	Still present	None
107	M/66Y	2.0	6	NA	Heart rate and rhythm disorders	Fibrillation atrial	Atrial fibrillation	None	Recovered	None
109	F/64Y	1.0	3	NA	Heart rate and rhythm disorders	Fibrillation atrial	Atrial fibrillation/ Flutter	None	Recovered	None
112	F/64Y	3.0	0	1:07	Respiratory system disorders	Pulmonary edema	Flash pulmonary Edema	None	Recovered	None
			0	1:07	Cardiovascular disorders General	Cardiac failure	Global ventricular Dysfunction	None	Recovered	None
116	M/71Y	3.0	1	NA	Respiratory system disorders	Respiratory insufficiency	Respiratory failure	None	Died	None
			1	NA	Heart rate and rhythm disorders	Tachycardia	Sinus tachcardia	None	Died	None
			1	NA	Cardiovascular disorders general	Cardiac failure right	Right cardiac failure	None	Died	None
			1	NA	Respiratory system disorders	Pulmonary edema	Pulmonary edema	None	Died	None
			2	NA	Urinary system disorders	Renal function abnormal	Renal failure	None	Died	None
222	M/65Y	1.0	1	NA	Vascular (extracardiac) disorders	Cerebrovascular disorder	CVA	None	Still present	None
227	M/55Y	2.0	0	5:50	Heart rate and rhythm disorders	Bradycardia	Bradycardia due to Vasovagal episode	None	Recovered	None
			0	5:50	Respiratory system disorders	Apnea	Apnea	None	Recovered	Unlikely
070012/ 122	F/21mo	4.5	6	NA	GI system disorders	Esophagospasm	Esophageal obstruction	None	Recovered	None
070014/ 411	M/39Y	1.5	3	NA	Vascular (extracardiac) disorders	Thrombophlebitis	Congested flap Secondary to venous Thrombosis	None	Recovered	None
174205/ 2	F/45Y	1.0	0	1:00	Metabolic and nutritional Disorders	Acidosis	Acidosis	None	Recovered	Not related
174303/ 133	M/28	1.5	0	Unk	Respiratory system disorders	Bronchospasm	Bronchospasm	None	Recovered	Probable
174309/ 5	M/51	1.5	3	Unk	Vascular (extracardiac) disorders	Cerebrovascular disorder	Stroke	None	Still present	Not related

Study/ Subject	Gender/ Age	Dose Mg/kg	Day	Time	System Organ Class	Preferred Term	Investigator Term	Action Taken	Outcome	Study Drug Relation by Investigator
			0	Unk	Respiratory system disorders	Upper airway Obstruction	Upper airway Obstruction	None	recovered	Possible
<b>PLACEBO</b>										
070001/										
455	M/70Y	0	0	4:00	Centr & periph nervous system Disorders	Hemiplegia	Acute L. hemiplegia Post op	None	Still present	None
461	F/78Y	0	0	2:29	Heart rate and rhythm disorders	Cardiac arrest	Asystolic cardiac arrest	None	Data not Available	None
558	F/77Y	0	5	NA	Cardiovascular disorders,general	Cardio-respiratory arrest	None	Died	None	
<b>SUCCINYLCHOLINE</b>										
070005/										
356	M/69Y	1.0	5	NA	Heart rate and rhythm disorders	Atrial fibrillation	Atrial fibrillation	None	Recovered	None
070007/										
115	M/62y	1.0	8	NA	Resistance mechanism disorders	Abscess	Abdominal abscess	None	Recovered	None
416	F/40y	1.0	8	NA	Application Site Disorders	Cellulitis	Probable Incisional Cellulitis	None	Recovered	None
472	M/65Y	1.0	2	NA	Secondary Terms	Postoperative bleeding	Surgical evacuation of hematoma	None	Recovered	None
			1	NA	Platelet,bleeding & clotting Disorders	Thrombosis	Graft thrombosis	None	Recovered	unlikely
528	M/29Y	1.0	2	NA	Urinary system disorders	Urinary retention	Urinary retention	None	Recovered	Unlikely
			7	NA	Platelet bleeding & clotting Disorders	Epistaxis	Nasal epistaxis	None	Recovered	None
541	F/36Y	1.0	0	3:04	Urinary system disorders	Urinary retention	Inability to void Post-op	None	Recovered	Unlikely
174308/										
409	F/64Y	1.0	0	4:19	Heart rate and rhythm disorders	Fibrillation atrial	Arrhythmia complete Fibrillation auricular	None	Recovered	Unlikely
<b>ORG 9488</b>										
174206										
6	M/62	0.2	1	Unk	Respiratory system disorders	Respiratory insufficiency	Respiratory insufficiency	None	Recovered	Not related
<b>MIVACURIUM</b>										
070005										
119	F/24y	0.25	1	NA	Urinary system disorders	Urinary retention	Urinary retention	None	Recovered	None
<b>ROCURONIUM</b>										
070009										

Study/ Subject	Gender/ Age	Dose Mg/kg	Day	Time	System Organ Class	Preferred Term	Investigator Term	Action Taken	Outcome	Study Drug Relation by Investigator
112	M/60Y	0.6	0	Unk	Centr & periph nervous system Disorders	Hemiparesis	CVA	None	Recovered	possible
139	F/91Y	0.6	2	NA	Centr & periph nervous system Disorders	Hemiparesis	L. sided flaccidity/hemiparesis	None	Died	unlikely

Modified Sponsor's Tables 49 and 54, ISS p. 0171 and p. 0185

## SECTION 10.7 ADVERSE EVENTS

Table 91 and Table 92 present a description of adverse events in adult and pediatric patients. The AEs are presented for Org 9487/9488, placebo, succinylcholine and active controls.

Table 91: Incidence of Adverse Experiences in Adult and Geriatric Subjects ( $\geq 18$  YR)  
By WHOART System-Organ Class All Subjects Treated Group

DISORDER	Org 9487 N=1509(%)	PLACEBO N=84 (%)	SUCCINYL- CHOLINE N=572 (%)	OTHER ACTIVE CONTROL N=115 (%)	Org 9488 N=14 (%)
	ALL AEs	ALL AEs	ALL AEs	ALL AEs	ALL AEs
<b>CARDIOVASC DISORDERS</b>	108 (7.2)	3 (3.6)	47 (8.2)	6 (5.2)	0
Hypotension	92 (6.1)	2 (2.4)	37 (6.5)	5 (4.3)	0
Hypertension	17 (1.1)	0	13 (2.3)	1 (0.87)	0
ECG Abnormal	3 (0.2)	0	0	0	0
Cardiac Failure	1 (0.07)	0	0	0	0
Cardiac Failure Right	1 (0.07)	0	0	0	0
ECG Abnormal Specific	1 (0.07)	0	0	0	0
Cardio-Respiratory Arrest	0	1 (1.2)	0	0	0
<b>RESPIRATORY DISORDERS</b>	103 (6.8)	3 (3.6)	23 (4)	2 (1.7)	1 (7.1)
Bronchospasm	60 (4)	1 (1.2)	12 (2.1)	1 (0.87)	0
Hypoxia	12 (0.8)	0	5 (0.87)	0	0
Increased Airway Pressure	10 (0.66)	0	0	0	0
Hypoventilation	3 (0.2)	0	1 (0.17)	0	0
Pneumothorax	3 (0.2)	0	0	0	0
Pulmonary Edema	3 (0.2)	0	0	0	0
Respiratory Depression	3 (0.2)	0	0	0	0
Coughing	2 (0.13)	1 (1.2)	3 (0.52)	0	0
Respiratory Insufficiency	2 (0.13)	0	0	0	1 (7.1)
Apnea	2 (0.13)	0	0	0	0
Laryngismus	2 (0.13)	0	0	0	0
Dyspnea	1 (0.07)	1 (1.2)	0	0	0
Pharyngitis	1 (0.07)	0	1 (0.17)	1 (0.87)	0
Larynx Edema	1 (0.07)	0	1 (0.17)	0	0
Hyperventilation	1 (0.07)	0	0	0	0
Rhinitis	1 (0.07)	0	0	0	0
Sputum Increased	1 (0.07)	0	0	0	0
Upper Airway Obstruction	1 (0.07)	0	0	0	0
<b>HEART RATE/RHYTHM DISORDERS</b>	73 (4.8)	2 (2.4)	13 (2.3)	5 (4.3)	0
Tachycardia	37 (2.5)	1 (1.2)	3 (0.52)	0	0
Bradycardia	24 (1.6)	0	6 (1)	2 (1.7)	0
Extrasystoles	3 (0.2)	0	1 (0.17)	1 (0.87)	0
Atrial Fibrillation	2 (0.13)	0	2 (0.35)	1 (0.87)	0
Arrhythmia	2 (0.13)	0	1 (0.17)	1 (0.87)	0
Ventricular Fibrillation	2 (0.13)	0	0	0	0
Ventricular Tachycardia	2 (0.13)	0	0	0	0
Cardiac Arrest	1 (0.07)	1 (1.2)	0	0	0
Atrial Arrhythmia	1 (0.07)	0	0	0	0
Extrasystoles	1 (0.07)	0	0	0	0
Supraventricular Tachycardia	1 (0.07)	0	0	0	0
<b>GI DISORDERS</b>	40 (1.7)	0	21 (3.7)	5 (4.3)	0
Nausea	28 (1.2)	0	17 (3)	5 (4.3)	0

DISORDER	Org 9487 N=1509(%)	PLACEBO N=84 (%)	SUCCINYL- CHOLINE N=572 (%)	OTHER ACTIVE CONTROL N=115 (%)	Org 9488 N=14 (%)
	ALL AEs	ALL AEs	ALL AEs	ALL AEs	ALL AEs
Vomiting	24 (0.2)	0	16 (2.8)	3 (2.6)	0
Ileus	2 (0.13)	0	0	0	0
Abdominal Pain	1 (0.07)	0	0	0	0
GI Disorder NOS	1 (0.07)	0	0	0	0
Rectal Hemorrhage	1 (0.07)	0	0	0	0
Oral Hemorrhage	1 (0.07)	0	0	0	0
Tooth Disorder	1 (0.07)	0	0	0	0
<b>SKIN AND APPENDAGE DISORDER</b>	<b>25(1.7)</b>	<b>1 (1.2)</b>	<b>19 (3.3)</b>	<b>2 (1.7)</b>	<b>0</b>
Erythematous Rash	18 (1.2)	1 (1.2)	17 (3)	2 (1.7)	0
Urticaria	3 (0.2)	0	0	0	0
Pruritus	2 (0.13)	0	2 (0.35)	0	0
Increased Sweating	2 (0.13)	0	0	0	0
Rash	1 (0.07)	0	0	0	0
<b>BODY AS A WHOLE GENERAL DISORDERS</b>	<b>24 (1.6)</b>	<b>0</b>	<b>6 (1)</b>	<b>3 (2.6)</b>	<b>0</b>
Fever	9 (0.6)	0	3 (0.52)	1 (0.87)	0
Rigors	5 (0.33)	0	1 (0.17)	1 (0.87)	0
Back Pain	4 (0.27)	0	1 (0.17)	2 (1.7)	0
Chest Pain	2 (0.13)	0	0	0	0
Pain	2 (0.13)	0	0	0	0
Hypothermia	1 (0.07)	0	1 (0.17)	0	0
Asthenia	1 (0.07)	0	0	0	0
Fatigue	1 (0.07)	0	0	0	0
Peripheral Edema	1 (0.07)	0	0	0	0
Therapeutic Response	1 (0.07)	0	0	0	0
Decreased Leg Pain	0	0	0	0	0
<b>APPLICATION SITE DISORDERS</b>	<b>21 (1.4)</b>	<b>1 (1.2)</b>	<b>8 (1.4)</b>	<b>0</b>	<b>0</b>
Injection Site Reaction	18 (1.2)	1 (1.2)	5 (0.87)	0	0
Injection Site Pain	3 (0.2)	0	0	0	0
Paravenous Injection	1 (0.07)	0	1 (0.17)	0	0
Cellulitis	0	0	2 (0.35)	0	0
Implantation Complication	0	0	1 (0.17)	0	0
<b>CNS AND PNS DISORDERS</b>	<b>12 (0.8)</b>	<b>1 (1.2)</b>	<b>4 (0.7)</b>	<b>3 (2.6)</b>	<b>0</b>
Hypoesthesia	3 (0.2)	0	1 (0.17)	0	0
Hemiparesis	2 (0.13)	0	0	2 (1.7)	0
Hypertonia	2 (0.13)	0	0	0	0
Prolonged Neuromuscular Block	2 (0.13)	0	0	0	0
Headache	1 (0.07)	0	0	1 (0.87)	0
Migraine	1 (0.07)	0	0	0	0
Tetany	1 (0.07)	0	0	0	0
Hemiplegia	0	1 (1.2)	0	0	0
Dizziness	0	0	2 (0.35)	0	0
Vertigo	0	0	1 (0.17)	0	0
<b>URINARY SYSTEM DISORDERS</b>	<b>7 (0.46)</b>	<b>0</b>	<b>2 (0.35)</b>	<b>1 (0.87)</b>	<b>0</b>
Urinary Retention	3 (0.2)	0	2 (0.35)	1 (0.87)	0
Oliguria	2 (0.13)	0	0	0	0
Renal Function Abnormal	1 (0.07)	0	0	0	0
Urinary Tract Infection	1 (0.07)	0	0	0	0
<b>SECONDARY TERMS</b>	<b>7 (0.46)</b>	<b>0</b>	<b>2 (0.35)</b>	<b>0</b>	<b>1 (7.1)</b>
Prolonged Anesthetic Emergence	2 (0.13)	0	0	0	0
Surgical Complication	2 (0.13)	0	0	0	0

DISORDER	Org 9487 N=1509(%)	PLACEBO N=84 (%)	SUCCINYL- CHOLINE N=572 (%)	OTHER ACTIVE CONTROL N=115 (%)	Org 9488 N=14 (%)
	ALL AEs	ALL AEs	ALL AEs	ALL AEs	ALL AEs
Postoperative Bleeding	1 (0.07)	0	2 (0.35)	0	1 (7.1)
Difficult Anesthetic Procedure	1 (0.07)	0	0	0	0
Malpositioned Endotracheal Tube	1 (0.07)	0	0	0	0
<b>PLATELET, BLEEDING &amp; CLOTTING DISORDERS</b>	<b>6 (0.4)</b>	<b>0</b>	<b>2 (0.35)</b>	<b>0</b>	<b>0</b>
Thrombosis	2 (0.13)	0	1 (0.17)	0	0
Epistaxis	1 (0.07)	0	1 (0.17)	0	0
Coagulation Factor Decreased	1 (0.07)	0	0	0	0
Hemoperitoneum	1 (0.07)	0	0	0	0
Purpura	1 (0.07)	0	0	0	0
<b>MUSCULO-SKELETAL DISORDERS</b>	<b>4 (0.27)</b>	<b>0</b>	<b>9 (1.6)</b>	<b>1 (0.87)</b>	<b>0</b>
Myalgia	3 (0.2)	0	6 (1)	0	0
Muscle Weakness	1 (0.07)	0	0	0	0
Arthralgia	0	0	1 (0.17)	0	0
Arthritis	0	0	1 (0.17)	0	0
Arthrosis	0	0	1 (0.17)	0	0
Myositis	0	0	0	1 (0.87)	0
<b>VASCULAR EXTRACARDIAC DISORDERS</b>	<b>4 (0.27)</b>	<b>0</b>	<b>0</b>	<b>1 (0.87)</b>	<b>0</b>
Cerebrovascular Disorder	2 (0.13)	0	0	0	0
Cerebral Hemorrhage	1 (0.07)	0	0	0	0
Thrombophlebitis	1 (0.07)	0	0	0	0
Flushing	0	0	0	1 (0.87)	0
<b>REPRODUCTIVE DISORDERS FEMALE</b>	<b>2 (0.13)</b>	<b>0</b>	<b>1 (0.17)</b>	<b>0</b>	<b>0</b>
Pelvic Inflammation	1 (0.07)	0	0	0	0
Vaginal Bleeding	1 (0.07)	0	0	0	0
Uterine Hemorrhage	0	0	1 (0.17)	0	0
<b>VISION DISORDERS</b>	<b>2 (0.13)</b>	<b>0</b>	<b>1 (0.17)</b>	<b>0</b>	<b>0</b>
Corneal Ulceration	1 (0.07)	0	0	0	0
Miosis	1 (0.07)	0	0	0	0
Vision Abnormal	0	0	1 (0.17)	0	0
<b>METABOLIC AND NUTRITIONAL DISORDERS</b>	<b>1 (0.07)</b>	<b>1 (1.2)</b>	<b>1 (0.17)</b>	<b>0</b>	<b>0</b>
Acidosis	1 (0.07)	0	0	0	0
NPN Increased	0	1 (1.2)	0	0	0
Respiratory Acidosis	0	0	1 (0.17)	0	0
<b>RED BLOOD CELL DISORDERS</b>	<b>1 (0.07)</b>	<b>0</b>	<b>2 (0.35)</b>	<b>0</b>	<b>0</b>
Anemia	1 (0.07)	0	2 (0.35)	0	0
<b>HEARING AND VESTIBULAR DISORDERS</b>	<b>1 (0.07)</b>	<b>0</b>	<b>0</b>	<b>1 (0.87)</b>	<b>0</b>
Hearing Decreased	1 (0.07)	0	0	0	0
Ear Disorder NOS	0	0	0	1 (0.87)	0
<b>LIVER AND BILIARY SYSTEM DISORDERS</b>	<b>1 (0.07)</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
Cholelithiasis	1 (0.07)	0	0	0	0

DISORDER	Org 9487 N=1509(%)	PLACEBO N=84 (%)	SUCCINYL- CHOLINE N=572 (%)	OTHER ACTIVE CONTROL N=115 (%)	Org 9488 N=14 (%)
	ALL AEs	ALL AEs	ALL AEs	ALL AEs	ALL AEs
MYO ENDO PERICARDIAL & VALVE DISORDERS	1 (0.07)	0	0	0	0
Myocardial Infarction	1 (0.07)	0	0	0	0
PSYCHIATRIC DISORDERS	1 (0.07)	0	0	0	0
Confusion	1 (0.07)	0	0	0	0
RESISTANCE MECHANISM DISORDERS	0	0	1 (0.17)	0	0
Abscess	0	0	1 (0.17)	0	0

Modified Sponsor's Listing of Incidence of Adverse Experiences Appendix A.6.3.1 Vol 159

Table 92: Incidence of Adverse Experiences in Pediatric Subjects (<13 Years)

By WHOART System-Organ Class: All Subjects Treated Group

DISORDER	NEONATES Org 9487 N=39 (%)	INFANTS Org 9487 N=168 (%)	CHILDREN Org 9487 N=177 (%)	CHILDREN MIVACURIUM N=23 (%)
CARDIOVASCULAR DISORDERS	2 (5.1)	2 (1.2)	1 (0.56)	1 (4.3)
Hypotension	2 (5.1)	1 (0.6)	1 (0.56)	1 (4.3)
Cardio-Respiratory Arrest	0	1 (0.6)	0	0
SKIN AND APPENDAGE DISORDER	0	6 (3.6)	0	
Erythematous Rash	0	4 (2.4)	0	0
Rash	0	2 (1.2)	0	0
SECONDARY TERMS	3 (7.7)	2 (1.2)	0	0
Prolonged Anesthetic Emergence	2 (5.1)	1 (0.6)	0	0
Postoperative Bleeding	0	1 (0.6)	0	0
Unplanned Endotracheal Extubation	1 (2.6)	0	0	0
APPLICATION SITE DISORDERS	0	1 (0.6)	0	0
Injection Site Reaction	0	1 (0.6)	0	0
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS	0	1 (0.6)	0	0
Ptosis	0	1 (0.6)	0	0

Modified Sponsor's Listing of Incidence of Adverse Experiences Appendix A.6.3.2 Vol 159

NOTE: This reviewer requested the Sponsor define the terms *hypotension*, *hypertension*, *tachycardia*, *bradycardia* as used throughout the Integrated Summary of Safety. Sponsor replied March 3, 1999 as follows:

"The terms hypotension, hypertension, bradycardia and tachycardia were not defined by Organon in the ORG 9487 development program nor were these terms used by Organon to characterize cardiovascular changes or events. Investigator descriptions of adverse experiences were coded using the WHO-ART Dictionary. Organon did not establish any criteria for terminology used to report adverse experiences."

The most commonly reported adverse events in the adult and geriatric groups (frequency  $\geq 2\%$ ) were hypotension, bronchospasm, and tachycardia. The 6.1% incidence of hypotension was the most common adverse event. The incidence of hypotension in the Org 9487 subjects was similar to that in the succinylcholine group (6.5%) but markedly higher than those subjects receiving placebo (2.4%). Bronchospasm occurred at a 4% rate in the Org 9487 patients, almost double that of the succinylcholine group (2.1%) and over 3 times the rate of the placebo patients (1.2%). Tachycardia occurred in 2.5% of Org 9487 patients, 1.2% of placebo patients and 0.52% of succinylcholine patients.

Less commonly occurring adverse events in the adult and geriatric group (frequency  $\geq 1\%$  but  $< 2\%$ ) were hypertension, bradycardia, nausea, erythematous rash, and injection site reaction. The incidence of these events in the Org 9487 patients was equal to or less than the incidence of the same events in the comparator groups (placebo, succinylcholine or active controls).

The common adverse experiences (frequency  $\geq 2\%$ ) in pediatric subjects (neonates to  $< 13$  years) receiving Org 9487 mostly occurred in the neonate group. These events were hypotension (5.1%), prolonged anesthetic emergence (5.1%), and unplanned endotracheal extubation (2.6%). Erythematous rash (2.6%) was a common AE that only occurred in the infant age category.

A less commonly occurring AE (frequency  $\geq 1\%$  but  $< 2\%$ ) was non-erythematous rash (1.2%) occurring in the infant age category.

## SECTION 10.8 NEWBORNS

Table 93: Incidence of Adverse Experiences in Newborn Subjects - All Subjects Treated Group

System Organ Class/ Preferred Term	Treatment Group	
	Org 9487 N=20 All SAEs n (%)	Succinylcholine N=22 All SAEs n (%)
<b>NEONATAL AND INFANCY DISORDERS</b>	5 (25)	5 (22.7)
Resp Distress Syndrome Neonatal	4 (20)	4 (18.2)
Respiratory Depression Neonatal	1 (5)	1 (4.5)
Hypotonia Neonatal	1 (5)	0

System Organ Class/ Preferred Term	Treatment Group	
	Org 9487 N=20 All SAEs n (%)	Succinylcholine N=22 All SAEs n (%)
FETAL DISORDERS		
Anus Imperforate	1 (5)	0
	1 (5)	0
GI SYSTEM DISORDERS		
Vomiting	0	1 (4.5)
	0	1 (4.5)
SECONDARY TERMS		
Cyst NOS	0	1 (4.5)
	0	1 (4.5)

Modified Sponsor's Table 60 ISS Vol 153 p.0196

One study was conducted in the US (070006) in which the effects of Org 9487 were examined in neonates born to women who received Org 9487 or succinylcholine in rapid sequence induction for C-section surgery under general anesthesia. A total of 43 subjects (21 Org 9487 and 22 succinylcholine) were enrolled in the study at four sites. Assessments in the newborns included APGAR and Neuroadaptive Capacity scores, plasma levels of Org 9487 and its 3-OH metabolite (Org 9488), umbilical venous and arterial blood gases.

Newborns of mothers who received Org 9487 for caesarian section had adverse experiences comparable to the control group of mothers receiving succinylcholine for their caesarian sections. 4/20 newborns of Org 9487 group had respiratory distress syndrome vs 4/22 of the succinylcholine group. 1/20 newborn of the Org 9487 group had neonatal respiratory depression vs 1/22 of the succinylcholine group. Neonatal hypotonia (1/20) occurred in the Org 9487 group but not in the succinylcholine group.

Table 94 : APGAR Scores Org 9487 and Succinylcholine Exposed Newborns

Newborn Assessment	Org 9487 2.5mg/kg	Succinylcholine 1.5mg/kg
One Minute Post Delivery		
N	19	22
Mean ± SD	7.4(1.8)	7.3(1.5)
Median	8	7.5
Range	3-9	4-9
Five Minutes Post Delivery		
N	19	22
Mean ± SD	8.5(.09)	8.6(.09)
Median	9	9
Range	6-10	6-10

Modified Sponsor's Table 105 Vol 153 p. 0301

The mean and median as well as the ranges of APGAR scores were similar in the Org 9487 and succinylcholine groups. Five infants in both treatment groups had respiratory distress noted. 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.

The following is a review of newborns who experienced difficulty after their mothers received Org 9487 for C-Section:

APGAR: Measured at 1 and 5 minutes (Heart Rate, Respiration, Muscle Tone, Reflex Irritability, Color)

Table 95: APGAR Scores in Newborns with difficulty at birth of mothers given Org 9487

Subject:	APGAR ONE MINUTE					APGAR FIVE MINUTES				
	Heart Rate	Resp	Muscle Tone	Reflex Irritability	Color	Heart Rate	Resp	Muscle Tone	Reflex Irritability	Color
109	2	2	1	1	2	2	2	2	1	2
114	1	0	0	1	1	2	1	1	1	1
308	1	1	1	2	2	1	1	2	2	2
310	1	1	0	1	0	2	2	1	1	1
313	2	1	1	2	1	2	2	2	2	1

### SECTION 10.8.1 NEWBORN SUBJECTS WITH DIFFICULTY AT BIRTH

- 109: 36 weeks gestation. Respiratory distress at birth. Admitted to ICU because of pneumonia; culture negative. Treated with O<sub>2</sub>, antibiotics. Discharged.  
Umbilical blood gases at birth: Arterial: pH 7.30, pCO<sub>2</sub> 53, pO<sub>2</sub> 18  
Venous: pH 7.37, pCO<sub>2</sub> 44, pO<sub>2</sub> 42
- 114: 38 weeks gestation. Respiratory distress at birth; intubated and admitted to ICU. Recovered in 12 hours. Born with Imperforate anus. (subject narrative Vol 121 p. 0122) The baby was delivered 22 minutes after the induction of the mother. The APGAR was 3 at 1 minute (absent respirations), 6 at 5 minutes and 8 at 10 minutes. He was noted to be floppy with an oxygen saturation of 70%. Muscle tone was lacking at the time of delivery. O<sub>2</sub> was administered by mask with positive pressure ventilation; the baby was intubated in the ICU and placed on mechanical ventilation. The next day the baby underwent a sigmoid colostomy for imperforate anus.  
Umbilical blood gases at birth: Arterial: pH 7.22, pCO<sub>2</sub> 67, pO<sub>2</sub> 10  
Venous: pH 7.24, pCO<sub>2</sub> 64, pO<sub>2</sub> 28
- 308: 39 weeks gestation. Poor respiratory effort and tone at birth; respiratory depression.  
Umbilical blood gases 3 min after birth: Arterial: pH 7.24, pCO<sub>2</sub> 62, pO<sub>2</sub> 15  
Venous: pH 7.27, pCO<sub>2</sub> 54, pO<sub>2</sub> 25
- 310: 39 weeks gestation. Respiratory distress, cyanosis, and heart rate < 100 at birth. Difficulty in baby extraction. Treated with Bag O<sub>2</sub>, suction, stimulation. Transferred to NICU.  
Umbilical blood gases at birth: Arterial: N/A

Venous: pH 7.23, pCO<sub>2</sub> 59, pO<sub>2</sub> 23

313: 38 weeks gestation: Immediately after delivery baby cyanotic with hypotonia and slow respirations. Secretions in the airway. Treated with suction, stimulation, bag O<sub>2</sub> and transferred to ICU.

Umbilical blood gases 5 min after birth: Arterial: pH 7.27, pCO<sub>2</sub> 56, pO<sub>2</sub> 17  
Venous: pH 7.26, pCO<sub>2</sub> 60, pO<sub>2</sub> 19

### SECTION 10.8.2 UMBILICAL BLOOD GASES

Table 96: Summary of Umbilical Artery and Venous Blood Gases: Study 070006:  
All Subjects Treated Group

Treatment Group	Blood Gas Parameter						
	pH	PCO <sub>2</sub> mmHg	PO <sub>2</sub> mmHg	O <sub>2</sub> Sat %	Base Excess MEq/l	HCO <sub>3</sub> Mmol/l	Hematocrit %
Org 9487 2.5 mg/kg							
Umbilical Arterial							
N	18	18	18	13	17	18	10
Mean (SD)	7.3(0)	58.4(10.5)	19.6(6.6)	34.5(22)	-1.3 (2.4)	25.7(3.7)	38.1(5.9)
Median	7.3	57	19	32	-2	25.8	37.3
Range	7.2-7.4	41-78	10-33	7-64	-5-4.2	19-33.6	31.8-52.2
Umbilical Venous							
N	18	18	19	13	17	18	10
Mean (SD)	7.3(0)	53.6(8)	31(12.9)	55.1(16.9)	-2.1(1.9)	24.7(2.1)	39.4(6.7)
Median	7.3	53	28	60	-2	24.9	39
Range	7.2-7.4	43-74	19-77	22-79	-5.5-1.0	21.6-28.2	26.1-52.2
Succinylcholine 1.5 mg/kg							
Umbilical Arterial							
N	20	20	20	15	18	20	11
Mean (SD)	7.3(.01)	54.9(14.1)	25.3(11.9)	37.5(17.8)	-2.3(4.8)	24.3(5.5)	40.3(6.6)
Median	7.3	56.5	23	34	-1.1	24.8	42
Range	7.0-7.3	32-90	6-63	3-73	-10-6.5	15-35.2	26.2-47
Umbilical Venous							
N	22	22	22	17	19	22	10
Mean (SD)	7.3(0)	47.7(7.2)	35.4(6.9)	61.2(13.5)	-2.3(2.5)	23.2(2.9)	39.9(6.6)
Median	7.3	48	35	62	-1.7	24.1	41.8
Range	7.2-7.4	34-64	24-50	24-80	-7-2.2	18-29.1	26.2-48

Sponsor's Table 106 Vol 153 p. 0302

The umbilical arterial and venous blood samples were obtained for blood gas analysis within 20 minutes of delivery. As compared to the succinylcholine control group, the Org 9487 exposed newborns were noted to have:

- Higher mean and median umbilical artery and venous pCO<sub>2</sub>
- Lower mean and median umbilical artery and venous pO<sub>2</sub>

### SECTION 10.8.3 PLACENTAL TRANSFER

The venous umbilical/maternal concentrations of Org 9487 and Org 9488 demonstrate that there was placental transfer of the drug from the maternal to fetal blood. The

umbilical/maternal ratios for Org 9487 ranged from 1.8 to 16.1 and the ratio for Org 9488 ranged from 1.7 to 19.9. The highest umbilical concentration of Org 9487 (venous sample) in a newborn was 1145.3 ng/mg (newborn 314) and the highest Org 9488 concentration (venous sample) was 86.7 ng/mg (newborn 102). In comparison, maternal levels at delivery (a median of 12 minutes after administration of Org 9487) ranged from about 4900 to 15,400 ng/mg and Org 9488 values ranged from about 400 (subject 100) to 840 ng/ml. Umbilical venous concentrations were higher than arterial samples except in newborn 202 and 308. When these newborns were excluded, the umbilical/maternal concentrations (%) for Org 9487 ranged from 4.4 to 16.1 and for Org 9488 the range was 4.6 to 19.9.

The highest umbilical/maternal concentration (%) of Org 9487 was observed in S 114 (16.1%, maternal level of 4867 ng/ml, umbilical level of 783.1 ng/mg) who had 22 minutes from drug administration to delivery. [Medical Review note: Newborn 114 had respiratory distress at birth, intubated and admitted to ICU. Recovered in 12 hours. Born with imperforate anus.] The newborn who was exposed to the maternal (subject 104) levels of Org 9487 for the longest time, (27 minutes from administration to delivery) had an umbilical/maternal concentration of 5.5% with umbilical levels of 286.9 ng/ml compared to maternal levels of 5224 ng/mg at delivery. No adverse experiences were noted for the newborn (subject 314) with the highest umbilical venous concentration (1145.3 ng/mg) nor were any adverse experiences noted for newborn 102 who had the highest umbilical venous level of Org 9487 (86.7 ng/ml). Maternal subjects 202 who received an overdose (5 mg/kg) did not have plasma samples drawn at delivery. The newborn had Org 9487 umbilical arterial levels of 1276.5 ng/mg and umbilical venous levels of 583.9 ng/mg. These concentrations are in the high range of the observation in the study. The fetus was exposed to maternal levels of Org 9487 during the 13 minutes from the time the overdose was administered to delivery.

## SECTION 10.9 SERUM CHEMISTRY PARAMETERS

Post surgical laboratory data were not collected in the following groups:

- Pediatric subjects
- Non US Phase 1, 2, and 3 studies

Table 97 Adult subjects  $\geq 18$  years

Laboratory Parameter	Criteria for Clinically Significant Abnormal Values	Treatment Group				
		Placebo	Org 9487 mg/kg			
			< 1.35	1.35-1.65	1.8-2.75	>2.75
N (%)	N (%)	N (%)	N (%)	N (%)		
Albumin	20% below LNL	6/22 (22)	10/101(10)	4/69(6)	8/94(9)	1/15(7)
Calcium	10% below LNL	6/27(22)	12/103(12)	5/70(7)	15/96(16)	0/15
Cholesterol (High Performance)	20% below LNL	3/27(11)	11/103(11)	2/70(3)	8/96(8)	5/15(33)
Creatine Kinase	3 Times above UNL	0/27	5/101(5)	2/69(3)	10/94(11)	8/15(53)
Serum Glucose	20% below UNL	4/27(15)	24/100(24)	8/69(12)	16/94(17)	3/15(20)
LDH	3 Times above UNL	0/23	1/97(1)	0/63	0/90	0/14
Phosphorus	10% above UNL	0/23	1/96(1)	0/62	1/89(1)	0/14
	10% below LNL	1/23 (4)	0/96	2/62(3)	0/89	0/14
Serum potassium	10% below LNL	0/23	1/97(1)	0/63	0/90	0/14
AST (SGOT)	3 Times above UNL	0/27	1/102(1)	0/69	2/95(2)	0/15
ALT (SGPT)	3 Times above UNL	0/27	1/102(1)	0/69	0/95	0/15
Total protein	20% below LNL	5/27(19)	16/103(16)	3/70(4)	6/96(6)	1/15(7)
Creatinine	$\geq 2.0$ mg/dl	0/27	1/103(1)	0/70	0/96	0/15

UNL= Upper Normal Limit

LNL= Lower Normal Limit

Table based on Sponsor's Table 89 ISS p. 0270

The studies that were included in the determination of laboratory chemistries were: 070001, 070003, 070004, 070005, 070011.

These studies can be briefly summarized as follows:

- 070001: Adults 18-85 having general surgery
- 070003: Adults having shunts inserted for dialysis
- 070004: Adults having general surgery
- 070005: Adults receiving balanced general anesthesia
- 070011: Adults 18-73 undergoing general surgery

With the exception of creatine kinase (CK), the incidence of clinically significant changes in chemistry parameters did not increase as a function of increasing Org 9487 dose and did not differ in a systematic way from that observed in the placebo group. The changes in the CK are striking: the subjects who received Org 9487 exhibited a marked elevation of the CK that appeared to essentially follow a dose-response pattern. None of the placebo subjects had an elevation of the CK; 53% of the patients who received the highest dose of Org 9487 had an elevation of their creatine kinase.

An inquiry to the sponsor for a possible explanation of the CK values resulted in the following response March 1, 1999:

"... the subjects in Study 070011 represent 76% (19/25) of all of the cases of elevated creatine kinase. Forty percent (19/47) of the subjects in this study had clinically significant levels of creatine kinase defined as three times the upper normal level. Subjects in this study were administered doses of 1.0, 2.0, or 3.0 mg/kg of Org 9487. The subjects in Study 070011 were in general older and

sicker than the average subjects in the development program, with a mean age of 60 to 64, and 60% to 75% ASA Class 3 in the three dose groups. These subjects were also undergoing a surgical procedure or had a physical condition which required the placement of an arterial cannula since the design of the study required that plasma samples for histamine be drawn from a cannula. These subjects were undergoing invasive surgeries such as thoracotomy or nephrectomy which cause a large amount of muscle trauma and therefore, would elevate creatine kinase. However, it is much more likely that the elevated creatine kinase levels observed in Study 070011 were due not to Org 9487 drug-patient interaction but to study specific effects which may have differed from other studies, such as drawing the lab specimens or type of surgery. Thirteen of the 19 subjects in Study 070011 with elevated levels of creatine kinase had surgery involving the lungs. In addition to increase in creatine kinase due to muscle trauma or myocardial infarction, high serum creatine kinase levels can occur in patients with pulmonary infarction or pulmonary edema. When the subjects from Study 070011 are not included, there is no dose related creatine kinase response observed."

The sponsor replied (March 9, 1999 correspondence) that the composition of the placebo group in the creatine kinase study consisted of patients from study 070001.

These placebo-dosed subjects underwent the following surgical procedures:

Bilateral Inguinal herniorrhaphy	Total abdominal hysterectomy
Bilateral tubal reanastomosis	
Hysterectomy	Lumbar discectomy
Bladder neck suspension	Lumbar discectomy
Laparotomy with oophorectomy	Lumbar laminectomy
Myomectomy for uterine fibroids	Thoracic laminectomy for tumor resection
Rectocele repair	Transphenoidal hypophysectomy
Knee Arthroscopy	Bx femur
Knee Arthroscopy	Face lifting
ACL repair	Hip replacement
Knee Arthroscopy	Radical prostatectomy
Remove hardware Tibia	Total vaginal hysterectomy
Myomectomy for uterine myomas	Anterior and posterior vagino-sacro fixation on vaginal wall
Total abdominal hysterectomy	Exploratory laparotomy for abdominal mass

## SECTION 10.10 ADVERSE EVENTS BY AGE

Table 98: Incidence of Common Adverse Experiences by Age: US Phase 2 and 3 Studies

Treatment Group	Common AE	Age (years)			
		18-30 N (%)	31-40 N (%)	41-50 (%)	51-64 N (%)
Org 9487 N=564	Hypotension	N=130 3 (2.3)	N=161 5 (3.1)	N=129 7 (5.4)	N=144 28 (19.4)
	Bronchospasm	11(8.5)	9 (5.6)	3 (2.3)	2 (1.4)
Succinylcholine N=177	Hypotension	N=46 1(2.2)	N=54 4(7.4)	N=45 5(11.1)	N=32 8(25)
	Bronchospasm	0	0	1(2.2)	1(3.1)

Modified Sponsor's Table 90 ISS Vol 153 p. 0273

Table 99: Incidence of Common Adverse Experiences by Age: Non-US Phase 2 and 3 Studies

Treatment Group	Common AE	Age (years)			
		18-30 N (%)	31-40 N (%)	41-50 (%)	51-64 N (%)
Org 9487 N=736	Hypotension	N=219 2(0.9)	N=183 2(1.1)	N=140 4(2.9)	N=194 9(4.6)
	Bronchospasm	10(4.6)	7(3.8)	4(2.9)	10(5.2)
Succinylcholine N=322	Hypotension	N=86 2(2.3)	N=87 0	N=69 2(2.9)	N=80 4(5.0)
	Bronchospasm	3(3.5)	3(3.4)	2(2.9)	1(1.3)

Modified Sponsor's Table 91 ISS Vol 153 p. 0274

In both the US and Non-US studies, the incidence of hypotension increased with age for subjects treated with Org 9487 or succinylcholine. Except for the highest age group in the Non-US studies, the incidence of bronchospasm decreased with advancing age for Org 9487 patients. For succinylcholine, bronchospasm was noted to decrease with advancing age only in the non-US studies.

### SECTION 10.11 ADVERSE EVENTS BY GENDER

In the US studies, the rates of hypotension, bronchospasm, and nausea in the Org 9487 treated subjects were approximately 2 to 3 fold higher among the male subjects compared to the females. In non-US studies, hypotension was higher among females; bronchospasm was slightly higher in the male group.

### SECTION 10.12 ADVERSE EVENTS BY RACE

Race was categorized as Caucasian and Non-Caucasian in the US studies. In Non-US studies race was not recorded in many of the studies; for subjects with data, the majority were Caucasian. The only AE with a relationship to race was bradycardia, the event occurring at nearly three times the incidence among Caucasians as compared to Non-Caucasians.

### SECTION 10.13 ADVERSE EVENTS BY ASA CLASS

In the US studies, the incidence of hypotension in the Org 9487 subjects was similar among ASA class 2 (11%) and ASA class 3-4 (10.2%) but higher compared to those of ASA 1 (4.4%). As in the US studies, the incidence of hypotension in the Non-US studies was higher among the Org 9487 subjects of ASA class 2 and 3-4 compared to those of ASA class 1 (5.8% and 2.6% vs 1.0%).

### SECTION 10.14 ADVERSE EVENTS BY INCREASING DOSE

Table 100: Incidence of Common AEs by Initial Dose of Org 9487 US and Non-US Adult Studies (18-64 years): All subjects Treated Group (Cutoff Date Oct 10, 1997)

Initial Dose of Org 9487 mg/kg				
Common Adverse Event	<1.35 N (%)	1.35-1.65 N (%)	1.7 to 2.75 N (%)	>2.75 N (%)
US STUDIES	N=79	N=322	N=150	N=13
Hypotension	3(3.8)	25(7.8)	10(6.7)	5(38.5)
Bronchospasm	1(1.3)	13(4)	9(6)	2(15.4)
Bradycardia	2(2.5)	8(2.5)	7(4.7)	0
Nausea	2(2.5)	8(2.5)	2(1.3)	0
NON-US STUDIES	N=43	N=632	N=35	N=25
Hypotension	0	16(2.5)	1(2.9)	0
Bronchospasm	1(2.3)	26(4.1)	2(5.7)	2(8.0)
Tachycardia	0	23(3.6)	0	0
Injection Site Reaction	0	16(2.5)	1(2.9)	0
Bronchospasm/ Increased Airway Pressure	3(7.0)	33(5.2)	3(8.6)	2(8)

Sponsor's Table 97 ISS Vol 153 p.0281

The incidence of hypotension, which increased with increasing dose, was particularly notable in the US studies. In both US and Non-US studies, bronchospasm dramatically increased with increasing dose. Bronchospasm and hypotension were the two adverse

events that were common (occurred with an incidence  $\geq 2\%$  in Org 9487 treated adult subjects) in both US and Non-US studies.

## **SECTION 10.15 ADVERSE EVENTS BY DRUG-DRUG INTERACTIONS**

### **SECTION 10.15.1 NON-ANESTHETIC MEDICATION INTERACTION**

Among the most commonly used concomitant medications given to Org 9487 treated subjects were vasoactive agents, anti-asthmatics, antihistamines, and systemic corticosteroids. These medications may have been administered before, after, or during the adverse event.

In the US studies, subjects taking concomitant vasoactive agents had an increased incidence of bronchospasm and hypotension compared to subjects not taking these agents (9.1% vs 4.6% and 11.4% vs 7.2%, respectively). In the Non-US studies, the incidence of bronchospasm did not vary as a function of vasoactive drug use.

Subjects taking concomitant anti-asthmatic drugs had a markedly larger incidence of bronchospasm compared to subjects not taking these agents (US: 61.9% vs 2.5%, Non-US: 35.3% vs 2.6%). The subjects in the Non-US studies also had a larger incidence of increased airway pressure (44.1% vs 3.5%). Since anti-asthmatic drugs were often used to treat the bronchospasm, this does not suggest an interaction between Org 9487 and anti-asthmatics.

Subjects using concomitant antihistamines had a higher incidence of hypotension compared to subjects who did not use these drugs (US: 14.6% vs 6.9%, Non-US: 9.1% vs 2.1%).

### **SECTION 10.15.2 ANESTHETIC MEDICATION INTERACTION**

The sponsor explored the possibility of interactions between Org 9487 and fentanyl, alfentanil, propofol, and thiopental. These were the most frequently used induction agents.

In the US studies, subjects who received fentanyl for induction had a higher incidence of each of the four common AEs compared to those who did not. Hypotension occurred in 8.3% of subjects who received fentanyl compared to 1.7% of those who did not. Bronchospasm occurred in 5.6% of subjects who received fentanyl compared to 0% of those who did not. Bradycardia occurred in 3.6% of subjects who received fentanyl compared to 1.7% who did not, and nausea occurred in 2.7% of subjects who received fentanyl compared to 0% who did not. In the Non-US studies, subjects who received fentanyl had an incidence of tachycardia of 4.8% compared to 0.8% of those who did not.

Alfentanil was only used in the Non-US studies. For subjects who received this agent, the incidence of bronchospasm, hypotension, and bronchospasm/increased airway pressure was greater (6.1% vs 3.2%, 4.9% vs 0.9%, and 8.6% vs 3.9% respectively).

In the US studies, subjects who received propofol for induction had a higher incidence of bradycardia compared to those who did not receive propofol (4.2% vs 1.45). For the Non-US studies, patients who received propofol had a higher incidence of bronchospasm and hypotension than subjects who did not (5.1% vs 3.8% and 5.5% vs 0.75, respectively).

#### **SECTION 10.16 PATIENTS WITH RENAL DYSFUNCTION**

Subjects with end stage renal disease were enrolled in two studies, 25 renal and 24 control. Overall percentage of AEs reported in renal subjects is slightly higher than those in the control group. Two renal patients had bronchospasm compared to one control. Tachycardia and hypotension were reported in one subject in each group.

#### **SECTION 10.17 PATIENTS WITH HEPATIC DYSFUNCTION**

15 adult cirrhotic subjects and 29 controls were enrolled in 3 studies. No adverse events were reported for any of the subjects with hepatic impairment.

#### **SECTION 10.18 PATIENTS WITH CARDIOVASCULAR DISEASE**

Subjects with coronary or valvular cardiovascular disease were enrolled in 2 studies (Org 9487 exposed N=32, 3 control groups N=65). There was no clear trend for adverse events specific to the Org 9487 group.

#### **SECTION 10.19 HISTAMINE RELEASE**

Plasma histamine release was assessed in one US study. In this study (070011), Org 9487 was administered as a 5 second rapid IV bolus. Plasma samples were taken at 5 time points: before, induction, before administration of Org 9487 (after induction), 3, and 5 minutes after administration of 1.0, 2.0, and 3.0 mg/kg of Org 9487. 47 subjects were treated. Clinically significant histamine levels were defined as  $\geq 1.0$  ng/mg or 100% increase from baseline in each of the 3 dose groups.

The elevation in histamine levels across the three treatment groups appear to be dose related with 6% (1/16), 13% (2/15), and 40% (6/15) of the subjects in the 1.0 mg/kg, 2.0 mg/kg and 3.0 mg/kg respectively demonstrating clinically significant histamine levels.

## SECTION 10.20 120 DAY SAFETY UPDATE

### SECTION 10.20.1 OVERVIEW

The Integrated Summary of Safety, part of NDA 20-984 submitted in June 1998, included data up to the cut-off date of October 10, 1997. The 120 Day Safety update presents analysis of safety data collected from October 11, 1997 through April 30, 1998. The update provides additional data on subjects from 5 studies. The combined studies had a total of 66 patients enrolled. Of these 66 subjects (63 received Org 9487), 52 were adults, 1 was a geriatric subject, and 13 were pediatric subjects (10 infants and 3 children [2-12 years]). 10 Org 9487 subjects were ASA 3 and 2 were ASA 4; the remaining Org 9487 subjects were ASA 1 or 2.

All subjects received a single bolus dose except those individuals in Study 174310 and Study 070014; these subjects received a single bolus dose followed by an Org 9487 infusion. The doses used in the adult and the geriatric subjects were within the range of 1.35 – 1.65 mg/kg. In the pediatric population, 40% received doses > 1.65 to 2.75 mg/kg and 60% received initial doses >2.75 mg/kg. 5 of the 10 infants and one of the 3 children received IM doses.

Table 101: Overview of Subjects with AEs by Age Group (US Studies)  
All Subjects Treated Group Dates: October 11, 1997-April 30, 1998

	Age Group			
	Adults 18-64 Yr N=6 n(%)	Geriatrics ≥ 65 Yr N=1 n(%)	Infants 1mo-<2 Yr N=10 n(%)	Children 2yr-≤12Yr N=3 n(%)
Subjects with AEs	3(50)	0	4(40)	0
Deaths	0	0	0	0
Subjects with SAEs	0	0	1	0
Subjects Discontinued Due to an AE	0	0	0	0

Modified Sponsor's Table 10, 120 Day Safety Update p. 0031

N=Number of subjects in the age group

n= Number of subjects who experienced an adverse or serious adverse event

Table 102: Overview of Subjects with AEs (Non-US Studies)  
 All Subjects Treated Group Dates: October 11, 1997-April 30, 1998  
 (Non-US Studies comprised of 18-64 year old subjects)

	Treatment Group	
	Org 9487 N=43 n(%)	Vecuronium N=3 n(%)
Subjects with AEs	10(23)	2(67)
Deaths	1(2)	0
Subjects with SAEs	2(5)	0
Subjects Discontinued due to an AE	0	0

Modified Sponsor's Table 11, 120 Day Safety Update p. 0032

N=Number of subjects in the age group

n= Number of subjects who experienced an adverse or serious adverse event

### SECTION 10.20.2 DEATHS

One 42 year old subject who received Org 9487 in the Non-US Study 174304 expired. The patient experienced a head injury leading to herniation of the brain. The day after admission the patient received a single dose of Org 9487 and underwent a craniotomy for evacuation of a hematoma. Six days after surgery, the cerebral edema was aggravated. The following day the patient experienced a cardiac arrest secondary to uncal and tonsillar herniation and died.

### SECTION 10.20.3 DISCONTINUATIONS

There were no subjects that were discontinued prior to or after receiving treatment with Org 9487 or the active control agent.

### SECTION 10.20.4 SERIOUS ADVERSE EVENTS

Study 070012 (subject 161):

6 month old male underwent a pyeloplasty under general anesthesia with Org 9487. Three days later he was discharged home. A week later he was readmitted due to an anastomotic leak from his previous pyeloplasty.

Study 174304 (subject 207):

This patient discussed in section on Intracranial Pressure.

### SECTION 10.20.5 ADVERSE EVENTS

In the group of Org 9487 treated adult subjects, the adverse events most often noted were 6 incidents of hypotension; there was one episode of tachycardia. In the pediatric population the only event probably related to Org 9487 was rash. There was one possible histamine related event: a 7 month old infant (Study 070012) experienced an area of induration at the site of the IM injection of Org 9487.

## SECTION 10.20.6 EFFECTS ON INTRACRANIAL PRESSURE

Study 174304 is evaluating the effects of Org 9487 on intracranial pressure. Either 1.5 mg/kg Org 9487, 0.1 mg/kg vecuronium or placebo were administered as a single bolus dose. Intracranial pressure measurements were done intraventricularly and were recorded just prior to administration of study drug, at 1,2,3,4,5,6,7,8,9,10 and 15 minutes after administration of the study drug. A total of 18 patients were enrolled, 7 in the Org 9487 group; 8 in the vecuronium group, and 3 in the placebo group.

Table 103: Summary Statistics of Changes of Baseline ICP Study 174304  
All Subjects Treated Group (Dates = Oct 11, 1997-April 30, 1998)

Statistical Parameter	Baseline (mmHg)	Change from Baseline (mmHg)										
		1 min	2 min	3 min	4 min	5 min	6 min	7 min	8 min	9 min	10 min	15 min
<b>Org 9487 1.5 mg/kg</b>												
N	7	7	7	7	7	7	7	7	7	7	7	7
Mean	14	-1	1	3	3	3	4	1	1	0	0	0
SD	5	1	7	7	7	8	8	2	1	1	1	1
Median	11	-1	-1	0	0	1	0	0	0	0	0	0
Min	8	-2	-3	-1	-2	-2	0	-1	0	-1	0	-1
Max	24	0	17	18	19	22	21	6	3	2	1	2
<b>Vecuronium 0.1 mg/kg</b>												
N	8	8	8	8	8	8	8	8	8	8	8	8
Mean	10	0	1	1	2	2	3	3	1	1	3	-1
SD	7	1	2	3	5	6	7	7	2	2	6	4
Median	9	0	1	0	1	0	0	0	1	1	2	-1
Min	3	-1	0	-1	-1	-1	-1	-2	-1	-1	-1	-8
Max	26	2	4	9	13	16	18	19	4	4	16	5
<b>Placebo</b>												
N	3	3	3	3	3	3	3	3	3	3	3	2
Mean	11	1	1	1	1	1	2	2	2	2	3	2
SD	1	1	2	3	3	3	2	3	3	4	4	2
Median	11	1	0	1	1	1	1	2	1	2	3	2
Min	10	0	-1	-1	-1	-1	0	-1	-1	-1	-1	0
Max	12	1	3	4	4	4	4	5	5	6	6	3

Note: All subjects enrolled in this study, including subjects reported on in the ISS, are included in this table.

The data for this table was derived from Appendices A.6.5 and A.6.6.

Baseline = Time of muscle relaxant administration.

Data were not recorded for subject #2 (placebo) at 15 min after MR.

### Sponsor's Table 21, 120 Day Safety Update

The least amount of change in the ICP readings was in the placebo group. The range of mean changes for ICP in the Org 9487 group was -1 to 4 mmHg; the range of mean changes for ICP in the vecuronium group was -1 to 3 mmHg. While the ICP measurements were fairly consistent across all time points for all 3 treatment groups, a patient in the Org 9487 group developed marked elevation of ICP two minutes after

receiving the drug. This particular patient may account for the maximum change from baseline (and markedly increased Standard Deviation) at the 2 and 3 minute intervals in the Org 9487 patients as compared to the Vecuronium or placebo patients. Sponsor reports (120-Day Safety Update, p 0033) that an increased ICP of 45 mmHg was also noted as an AE in one subject in this study who received vecuronium.

**CRF Study 174304 (Subject 207):**

18 year old 74.7 kg male with traumatic head injury. Patient was intubated and sedated with propofol and alfentanil before Org 9487 administration. Prior to 120 mg of Org 9487, stable clinical conditions were present with T4/T1 ratio  $\geq 0.8$ , ICP = 16 mmHg, CPP = 69 mmHg, arterial BP = 142/65.

Two minutes after receiving Org 9487, the ICP increased from 17 to 39 mm Hg. The event lasted for 5 minutes. The patient was treated with hyperventilation and increasing a dopamine infusion from 5 to 10  $\mu\text{g}/\text{kg}/\text{min}$ . The patient had a similar episode of transient increased ICP earlier the same day. Patient recovered.

**Table 104** Intracranial pressure measurements were as follows:

Time	Intracranial Pressure mmHg	Comment
Just before muscle relaxant	17	
1 minute following relaxant	17	
2 minutes following relaxant	34	
3 minutes following relaxant	35	
4 minutes following relaxant	36	
5 minutes following relaxant	39	
6 minutes following relaxant	38	Hyperventilation started Dopamine increased from 5 to 10 $\mu\text{g}/\text{kg}/\text{min}$
7 minutes following relaxant	23	
8 minutes following relaxant	19	
9 minutes following relaxant	17	
10 minutes following relaxant	18	
15 minutes following relaxant	17	

Table based on CRF Subject 207; received from Organon March 17, 1999

## SECTION 10.21 SAFETY DISCUSSION

While Org 9487 was reasonably well tolerated by most of the subjects enrolled in the studies, some issues regarding safety need addressed:

### SECTION 10.21.1 DEATHS:

The deaths of the patient with head trauma and the patient with sickle cell disease were most probably not related to Org 9487. The relationship of Org 9487 to the death of the 71-year-old man who underwent the thoracotomy is less clear. The blood pressure dropped more than 45% within 5 minutes after administration of Org 9487. Three days postoperatively the patient expired after experiencing respiratory failure, renal failure and right ventricular failure. The relationship of these three terminal events to the hypotension is unknown.

### **SECTION 10.21.2 COMMON ( $\geq 2\%$ ) ADVERSE EVENTS:**

Hypotension, the most common AE, occurred at a 6.1% incidence; this was similar to the 6.5% occurrence in the succinylcholine group but much higher than the subjects receiving placebo (2.1%).

The incidence of bronchospasm was 4% in the Org 9487 patients. This was double the incidence of the patients who received succinylcholine and triple the incidence of those in the placebo group.

Tachycardia occurred in 2.5% of Org 9487 patients, 1.2% of placebo patients and 0.52% of succinylcholine patients.

In the pediatric subjects, at a rate of 5.1%, hypotension and prolonged anesthetic emergence were the most commonly occurring adverse events. Unplanned endotracheal extubation and erythematous rash at an incidence of 2.6% were the adverse events next in order of occurrence.

Clinically significant levels of histamine were observed in a dose-response relationship after administration of Org 9487. The known effects of histamine release, tachycardia, bronchospasm, hypotension, and erythematous rash, may possibly explain the common adverse effects observed with Org 9487.

### **SECTION 10.21.3 NEWBORNS:**

While the mean and median as well as the ranges of APGAR scores were similar in the Org 9487 and succinylcholine groups, APGAR scores of 6 or less were given to 4 newborns at one minute in both groups. 4/20 Org 9487 exposed newborns had respiratory distress syndrome vs 4/22 of the succinylcholine group. One baby with a high umbilical blood level of Org 9487 was so hypotonic at birth that intubation and mechanical ventilation were required. The incidence of difficulties in the newborns of the Org 9487 exposed mothers, while similar to the active control group, is disturbing to this reviewer.

### **SECTION 10.21.4 ELEVATED CREATINE KINASE:**

Sponsor's explanation for the elevated CK levels (three times above normal in Org 9487 patients as compared to placebo controls) is that the Org 9487 exposed patients were older, sicker, and underwent more extensive surgery than the placebo patients. Data to validate this explanation has been requested and Organon has replied to this request

March 19, 1999. The reply will be reviewed and submitted as an addendum to the NDA Application.

Although differences in composition of the comparator groups may explain the difference in the obtained CK values, differences in composition of the groups does not explain the dose-response relationship in CK results in the patients who received Org 9487. Some non-depolarizing neuromuscular blocking agents that are based on a steroid nucleus have been associated with myopathy with prolonged infusion. The implications of the elevated creatine kinase after exposure to Org 9487 are unknown at this time.

#### **SECTION 10.21.5 ELEVATED INTRACRANIAL PRESSURE:**

In a patient with head trauma and steady-state clinical conditions, Org 9487 was associated with a rise in ICP from a normal 17 mmHg to 34 mmHg. The doubling in pressure occurred two minutes after drug administration. The patient was treated with hyperventilation and the pressure returned to normal 8 minutes following muscle relaxant.

#### **SECTION 10.21.6 LIMITED EXPOSURE IN SERIOUSLY ILL PATIENTS**

Table 105 Exposure in Seriously Ill Patients

	ASA 3	ASA 4	ASA 5
Adults	159	14	0
Pediatrics	2	0	0

There was very limited exposure of Org 9487 to seriously ill patients in either the adult/geriatric or pediatric populations. Considering that hypotension, bronchospasm and tachycardia are common adverse events after Org 9487 administration, it is unknown as to how seriously ill patients will tolerate this agent.

## SECTION 11 DISCUSSION

Org 9487 is an effective neuromuscular blocking agent for providing acceptable intubating conditions. In adults it is generally inferior to succinylcholine. Except for higher Org 9487 doses (which prolong duration), succinylcholine more frequently provides excellent intubating conditions. Only in a study where succinylcholine was not as effective as expected was Org 9487 equivalent for acceptable [excellent plus good] intubating conditions.

This reviewer agrees that Org 9487 possesses a unique property among non-depolarizing neuromuscular blocking agents in that its activity can be reversed at a deep level of blockade.

There are safety issues that warrant consideration:

- The database for the patients in the Caesarian Section group is small and the results of newborn exposure are troubling. Four out of twenty newborns had APGAR ratings of 6 or less. A newborn with a high umbilical blood level of Org 9487 required intubation and mechanical ventilation. The Org 9487 exposed babies had higher mean and median artery and venous umbilical PCO<sub>2</sub> and lower mean and median umbilical artery and venous PO<sub>2</sub>
- Some effects of Org 9487 make repeat dosing or dosing by infusion a concern:
  1. The greater than 2 week half-life and the presence of the drug six weeks after administration
  2. Prolongation of the QT Interval in animals during chronic dosing
  3. Elevation (3 times above normal) of the creatine kinase level in a dose-response fashion
  4. One patient displayed degradation of neuromuscular function after attaining evidence of adequate spontaneous recovery following an infusion of Org 9487

## SECTION 12 RECOMMENDATIONS

Except for use in obstetrics or infusion/bolus dosing, recommend approval of this agent.

/S/

Charles R. Cortinovis, MD MPH  
Medical Officer

**APPENDIX**

<b>ASA Class</b>	<b>Classification of physical status established by the American Society of Anesthesiologists</b>
<b>Class 1</b>	<b>There is no organic, physiologic, biochemical, or psychiatric disturbance. The pathologic process for which operation is to be performed is localized and is not a systemic disturbance.</b>
<b>Class 2</b>	<b>Mild to moderate systemic disturbance caused by the condition to be treated surgically or by other pathophysiologic processes.</b>
<b>Class 3</b>	<b>Severe systemic disturbance or disease, from whatever cause, even though it may not be possible to define the degree of disability with finality.</b>
<b>Class 4</b>	<b>Indicative of the patient with severe systemic disorder already life threatening, not always correctable by the operative procedure.</b>
<b>Class 5</b>	<b>The moribund patient who has little chance of survival but is submitted to operation in desperation.</b>

**NDA: #20-984**

**NAME: Raplon (Rapacuronium Bromide)**

**SPONSOR: Organon, Incorporated**

**REVIEW DATE: 08/16/99**

**TYPE OF REVIEW: Addendum to NDA**

**REVIEWER: Patricia Hartwell, MD MBA**

---

**ADDENDUM TO MEDICAL OFFICER REVIEW:**

**Part I – Labeling Addition**

Information from clinical study #07005, an open-label comparison of efficacy parameters between rapacuronium, succinylcholine, and mivacurium, was included in the "Clinical Studies" section of the label at the sponsor's request. A comparative table illustrating time to maximum block, peak effect %, clinical duration, 25-75% T1 recovery index, and time to 70% T4/T1 recovery was constructed with data from patients 18 years and older. Language describing the comparative onsets and duration of action was also added. All information included in the narrative and the table coincided with the stated efficacy endpoints for this study and was consistent with data provided by the sponsor in their NDA submission.

**Part II – Additional Patient Death**

*Study 070007 (Subject 280)*

Patient was a 72 yr old male with a history of hypertension, atrial fibrillation, chronic anticoagulation for a prosthetic mitrial valve, congestive heart failure, and hypothyroidism. He underwent a right hemicolectomy for a diagnosis of adenocarcinoma of the cecum and received 1 mg/kg succinylcholine for intubation. He did not receive ORG 9487. The surgery was uneventful and the patient remained clinically stable until 5 days post-operatively when he developed gastrointestinal bleeding and subsequent hypotension. At the time of this event the patient was anticoagulated with intravenous heparin and was also receiving prednisone and hydrocortisone. Despite discontinuation of these three medications, the hemorrhage and hypotension persisted. The patient suffered a cardiac arrest and died on the sixth post-operative day. This death was not related to ORG 9487 – patient received the active control.

### Part III - SAFETY UPDATE FOR PERIOD 04/30/98 THROUGH 02/28/99:

#### OVERVIEW:

The adverse event and death information submitted by the sponsor covering the period from the end of the 120 Day Safety Update to February 28, 1999 includes information on an additional 705 patients. The combined studies enrolled a total of 512 adults, 84 geriatric patients, 72 infants, 17 children, and 20 subjects designated "adults and geriatrics". No other demographic or dosing information is provided by the sponsor.

**Table 1: Overview of Subjects with Adverse Events by Age Group – US Studies  
All Subjects Treated Group, May 1, 1998 to February 28, 1999**

	Age Group			
	Adults 18-64 yr N=147 n (%)	Geriatrics ≥65 yr N=5 n(%)	Infants 1 mo - <2yr N=72 n (%)	Children 2 yr - ≤12yr N=17 n (%)
Subjects with AEs	55 (37)	3 (60)	34 (47)	8 (47)
Deaths	0	0	0	0
Subjects with SAEs	2 (1)	0	0	2 (12)
Subjects Discontinued Due to an AE	0	0	0	0
Modified Sponsor's Table 3, Additional Safety Update, p.02 N=number of subjects in age group n=number of subjects who experienced an adverse or serious adverse event				

**Table 2: Overview of Subjects with Adverse Events by Age Group – Non-US Studies  
All Subjects Treated Group, May 1, 1998 to February 28, 1999**

	Age Group		
	Adults 18-64 yr N=365 n (%)	Geriatrics ≥65 yr N=79 n(%)	Intradermal Adults & Geriatrics N=20 n (%)
Subjects with AEs	130 (36)	28 (35)	0
Deaths	0	1 (1)	0
Subjects with SAEs	30 (82)	2 (3)	0
Subjects Discontinued Due to an AE	10 (27)	0	0
Modified Sponsor's Table 4, Additional Safety Update, p.03 N=number of subjects in age group n=number of subjects who experienced an adverse or serious adverse event			

#### DEATHS:

##### *Study 174314 (Subject 5209)*

One 74 year old male patient who received a 2.5mg/kg dose of Org 9487 in the Non-US Study 174314 died. The patient, who had pre-existing hypertension, underwent a neck dissection for a malignant nasal tumor. Two minutes following a rapid sequence

induction with 150  $\mu$ g of fentanyl, 500 mg of thiopental, and 210 mg of ORG 9487 the patient became profoundly hypotensive, requiring treatment with at least 22.5 mg of ephedrine. Blood pressure apparently stabilized 14 minutes later. The evening of the day following surgery the patient experienced cardiac failure and hypotension. The patient subsequently died 7 days after surgery with sepsis and cardiovascular, respiratory, and renal failure. The investigators attribute the intraoperative hypotension to cardiovascular depression from thiopental and conclude that the study drug was not responsible because no evidence of histamine release was observed. The investigators conclude that the patient's death was secondary to multiple organ failure and was not attributable to the study drug.

On the basis of the information provided, this reviewer has made the following conclusions about the event. The patient was classified as ASA 2 on the preoperative assessment form and the only systemic problems noted were smoking 10 cigarettes/day and arterial hypertension for which the patient was taking an unknown medication. One month prior to surgery the patient's blood pressure was recorded as 136/93. This documented history would lead us to believe that, despite the presence of a malignant tumor and probable inadequate control of essential hypertension, the patient was in relatively good physical shape prior to undergoing the surgical procedure. Before the rapid sequence induction the patient's blood pressure was 178/95 and then a marked deterioration is noted following administration of thiopental and ORG 9487. The lowest blood pressure provided, 59/42, occurred 4 minutes after the study drug and required significant doses of a vasoconstrictor agent for resolution. The sponsor has explained this episode on the cardiac depressant effects of thiopental, certainly a possibility given the known effects of a large thiopental bolus.

However, from the data provided, it does not seem possible to totally discount ORG 9487 as a factor in this hypotensive episode. Minor histamine release may manifest as isolated vasodilation without rash or bronchospasm. In addition, hypotension has been reported in approximately 5% of subjects who have received ORG 9487 in clinical trials. A patient with a history of poorly-controlled hypertension, as appears to be the case on examination of this patient's baseline pressures, may become profoundly hypotensive with minimal vasodilating medications. This reaction may be secondary to an up-regulation of vascular receptors or simply to a relative hypovolemia from chronically increased systemic vascular resistance. The hypotensive episode as recorded was of an extent that it could have caused myocardial ischemia/infarction, resulting in the subsequent cardiac failure on the first post-operative day. It is impossible from the data provided to discern whether this episode of cardiac failure was the primary cause of the multi-system failure leading to the patient's death.

The information provided and the conclusions that may be drawn are not sufficient to warrant a labeling change or warning. This event may be coincidental and unrelated to the administration of ORG 9487. Close post-marketing surveillance for an increased incidence of hypotensive episodes associated with the use of ORG 9487 in hypertensive patients may provide more information in this area.

**DISCONTINUATIONS:**

There were two patients in non-US studies who were discontinued due to an adverse event:

*Study 174310 (Subject 513)*

- 57 yr old male received partial dose of 1.51 mg/kg of ORG 9487; developed hypotension prior to administration of study agent and administration aborted; no relationship to ORG 9487

*Study 174313 (Subject 31)*

- 19 yr old male received 1.52 mg/kg of ORG 9487; developed bronchospasm approximately 14.5 hours after administration of the study agent; possible relationship to ORG 9487

**SERIOUS ADVERSE EVENTS:**Non-Treated Subjects – US Studies:*Study 070013 (Subject 201)*

- 6 mo old male experienced an episode of bradycardia that resolved; patient did not receive the study drug

*Study 070013 (Subject 201)*

- 6 mo old male experienced an episode of hypoxia that resolved; patient did not receive the study drug.

*Study 070013 (Subject 201)*

- 6 mo old male experienced an episode of laryngospasm that resolved; patient did not receive the study drug

All-Subjects Treated – Non-US Studies*Study 174310 (Subject 513)*

- 57 yr old male received partial dose of 1.51 mg/kg of ORG 9487; developed hypotension prior to administration of study agent and administration aborted; no relationship to ORG 9487

*Study 174313 (Subject 31)*

- 19 yr old male received 1.52 mg/kg of ORG 9487; developed bronchospasm approximately 14.5 hours after administration of the study agent; possible relationship to ORG 9487

*Study 174314 (Subject 1229)*

- 59 yr old male received 2.0 mg/kg of ORG 9487; developed bronchospasm 1 minute after administration of the study drug which resolved; probable relationship to ORG 9487

*Study 174314 (Subject 5204)*

- 70 yr old male received 2.56 mg/kg of ORG 9487; developed bleeding on the second post-operative day; patient recovered

*Study 174314 (Subject 5209)*

- discussed in detail in section on Deaths

*Study 174313 (Subject 33)*

- 20 yr old female received 1.0 mg/kg of Succinylcholine; developed bleeding on the fourth post-operative day; patient recovered

All-Subjects Treated – US Studies*Study 070013 (Subject 153)*

- 3 yr old female ASA 1 with no relevant medical history received 4.84 mg/kg ORG 9487 after a halothane induction for chalazion excision; patient experienced prolonged neuromuscular blockade from this initial dose; patient received two doses of reversal agents at 22 and 38 minutes after administration of ORG 9487 and was extubated; patient continued with clinical weakness, requiring 100% O<sub>2</sub> with PEEP by face mask to maintain oxygen saturation; patient received a third dose of reversal agents 54 minutes after administration of ORG 9487; the patient was considered "clinically normal" 39 minutes after the third dose of reversal agents

*Study 070013 (Subject 156)*

- 44 month old male received 4.8 mg/kg ORG 9487; developed bronchospasm one minute after administration of the study drug which resolved; this event was possibly related to the study drug

*Study 070018 (Subject 305)*

- 41 yr old female with no relevant medical history received 2 mg/kg ORG 9487; reversal agents administered per protocol 2 minutes later and muscle relaxation maintained with rocuronium; reversal agents administered after rocuronium when 4 strong twitches present; clinically weak and remained intubated for approximately 5 hours after reversal agents; patient complained of some non-specific right-sided weakness the night of surgery and on the 7 day phone follow-up; neurology consult suspected underlying myopathy and scheduled work-up at a future date

*Study 070018 (Subject 318)*

- 23 yr old female with no relevant medical history received 1.50 mg/kg ORG 9487; reversal agents administered per protocol 2 minutes later and muscle relaxation maintained with rocuronium; reversal agents administered twice after rocuronium but

no information is provided as to EMG recording at this point; patient complained of weakness, was reintubated, and was finally extubated 2 hours 47 minutes after the dose of ORG 9487; investigator suspected weakness secondary to high dose of reversal agent administered however there is no documentation of partial resolution of motor activity after either ORG 9487 or rocuronium so it is not possible to eliminate these agents as causative

### ADVERSE EVENTS:

The following table quantifies the more commonly reported adverse events in US and non-US studies during the relevant time period:

**Table 3 Incidence of Adverse Events All- Subjects Treated Group, Raplon Subset (%)**

System-Organ Class	Adults & Geriatrics (≥ 18 yrs) N = 596	Children (2 to <12 yrs) N = 17	Infants (1 mo to < 2 yrs) N = 72
Gastrointestinal	5.7	5.9	2.8
Nausea	4.0		
Heart Rate and Rhythm	5.7	11.8	1.4
Tachycardia	3.7	11.8	
Bradycardia	1.0		
Respiratory	15.8	17.6	11.1
Bronchospasm	10.9	5.9	4.2
Cardiovascular	6.5	5.9	
Hypertension	2.0	5.9	
Hypotension	3.7		
General	0.8	5.9	5.6
Nervous System	0.8		1.4
Musculo-skeletal	0.3		
Skin	9.4		
Application Site	0.7	35.3	29

Upon comparison of this table with previously reported incidences for these adverse events, it is noted that, while most occur at the expected frequencies, bronchospasm in all age groups and application site reactions in infants have occurred more frequently and hypotension in adults has occurred less frequently. The following table illustrates these results.

**Table 4 Comparison of Adverse Event Incidence (%) – Present vs. Prior Data**

Adverse Event	Adults & Geriatrics		Children		Infants	
	Prior Data	Present Data	Prior Data	Present Data	Prior Data	Present Data
Bronchospasm	4	10.9	0	5.9	0	4.2
Application Site Reaction	1.4	.7	0	35.3	0.6	29
Hypotension	6.1	3.7	0.56	0	0.6	0

When the present and prior data sets are combined, bronchospasm in adults and application site reactions in infants and children continue to show a trend of increasing incidence from that reported in the prior data. The incidence of hypotension in adults, while still lower than that previously reported, is normalizing to the expected value. The following table illustrates these results.

**Table 5 Comparison of Adverse Event Incidence (%) – Pooled vs. Prior Data**

Adverse Event	Adults & Geriatrics		Children		Infants	
	Prior Data	Pooled Data	Prior Data	Pooled Data	Prior Data	Pooled Data
Bronchospasm	4	5.9	0	1	0	1.3
Application Site Reaction	1.4	1	0	3	0.6	13
Hypotension	6.1	5	0.6	0	0.56	0

From these analyses, it appears that the incidence of bronchospasm and application site reactions may be greater than originally suspected. Whether this trend is also an indication of a higher incidence of histamine related events can not be discerned at this time but bears watching in the post-marketing period. The incidence of all other adverse events as reported are consistent with previously reported data as incorporated into labeling claims.

Patricia Hartwell, MD MBA  
Medical Officer

CC: Division File  
Original NDA #20-984  
HFD-170 Patricia Hartwell, MD MBA  
HFD-170 R.A. Rappaport, MD  
HFD-170 Project Manager: Susmita Samanta

**PLEASE NOTE:**

**MEDICAL OFFICER'S REVIEW OF 4  
MONTH SAFETY UPDATE IS INCLUDED  
IN THE MEDICAL OFFICER'S ORIGINAL  
REVIEW**

**NDA: #20-984**

**NAME: Raplon (Rapacuronium Bromide)**

**SPONSOR: Organon, Incorporated**

**REVIEW DATE: 08/16/99**

**TYPE-OF-REVIEW: Addendum to NDA**

**REVIEWER: Patricia Hartwell, MD MBA**

---

**ADDENDUM TO MEDICAL OFFICER REVIEW:**

**Part I – Labeling Addition**

Information from clinical study #07005, an open-label comparison of efficacy parameters between rapacuronium, succinylcholine, and mivacurium, was included in the "Clinical Studies" section of the label at the sponsor's request. A comparative table illustrating time to maximum block, peak effect %, clinical duration, 25-75% T1 recovery index, and time to 70% T4/T1 recovery was constructed with data from patients 18 years and older. Language describing the comparative onsets and duration of action was also added. All information included in the narrative and the table coincided with the stated efficacy endpoints for this study and was consistent with data provided by the sponsor in their NDA submission.

**Part II – Additional Patient Death**

*Study 070007 (Subject 280)*

Patient was a 72 yr old male with a history of hypertension, atrial fibrillation, chronic anticoagulation for a prosthetic mitral valve, congestive heart failure, and hypothyroidism. He underwent a right hemicolectomy for a diagnosis of adenocarcinoma of the cecum and received 1 mg/kg succinylcholine for intubation. He did not receive ORG 9487. The surgery was uneventful and the patient remained clinically stable until 5 days post-operatively when he developed gastrointestinal bleeding and subsequent hypotension. At the time of this event the patient was anticoagulated with intravenous heparin and was also receiving prednisone and hydrocortisone. Despite discontinuation of these three medications, the hemorrhage and hypotension persisted. The patient suffered a cardiac arrest and died on the sixth post-operative day. This death was not related to ORG 9487 – patient received the active control.

### Part III - SAFETY UPDATE FOR PERIOD 04/30/98 THROUGH 02/28/99:

#### OVERVIEW:

The adverse event and death information submitted by the sponsor covering the period from the end of the 120 Day Safety Update to February 28, 1999 includes information on an additional 705 patients. The combined studies enrolled a total of 512 adults, 84 geriatric patients, 72 infants, 17 children, and 20 subjects designated "adults and geriatrics". No other demographic or dosing information is provided by the sponsor.

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Subjects with AEs	55 (37)	3 (60)	34 (47)	8 (47)
Deaths	0	0	0	0
Subjects with SAEs	2 (1)	0	0	2 (12)
Subjects Discontinued Due to an AE	0	0	0	0

Modified Sponsor's Table 3, Additional Safety Update, p.02  
N=number of subjects in age group  
n=number of subjects who experienced an adverse or serious adverse event

Table 2: Overview of Subjects with Adverse Events by Age Group – Non-US Studies  
All Subjects Treated Group, May 1, 1998 to February 28, 1999

	Age Group		
	Adults 18-64 yr N=365 n (%)	Geriatrics ≥65 yr N=79 n(%)	Intradermal Adults & Geriatrics N=20 n (%)
Subjects with AEs	130 (36)	28 (35)	0
Deaths	0	1 (1)	0
Subjects with SAEs	3 0.(82)	2 (3)	0
Subjects Discontinued Due to an AE	1 0.(27)	0	0

Modified Sponsor's Table 4, Additional Safety Update, p.03  
N=number of subjects in age group  
n=number of subjects who experienced an adverse or serious adverse event

#### DEATHS:

##### Study 174314 (Subject 5209)

One 74 year old male patient who received a 2.5mg/kg dose of Org 9487 in the Non-US Study 174314 died. The patient, who had pre-existing hypertension, underwent a neck dissection for a malignant nasal tumor. Two minutes following a rapid sequence

induction with 150  $\mu$ g of fentanyl, 500 mg of thiopental, and 210 mg of ORG 9487 the patient became profoundly hypotensive, requiring treatment with at least 22.5 mg of ephedrine. Blood pressure apparently stabilized 14 minutes later. The evening of the day following surgery the patient experienced cardiac failure and hypotension. The patient subsequently died 7 days after surgery with sepsis and cardiovascular, respiratory, and renal failure. The investigators attribute the intraoperative hypotension to cardiovascular depression from thiopental and conclude that the study drug was not responsible because no evidence of histamine release was observed. The investigators conclude that the patient's death was secondary to multiple organ failure and was not attributable to the study drug.

On the basis of the information provided, this reviewer has made the following conclusions about the event. The patient was classified as ASA 2 on the preoperative assessment form and the only systemic problems noted were smoking 10 cigarettes/day and arterial hypertension for which the patient was taking an unknown medication. One month prior to surgery the patient's blood pressure was recorded as 136/93. This documented history would lead us to believe that, despite the presence of a malignant tumor and probable inadequate control of essential hypertension, the patient was in relatively good physical shape prior to undergoing the surgical procedure. Before the rapid sequence induction the patient's blood pressure was 178/95 and then a marked deterioration is noted following administration of thiopental and ORG 9487. The lowest blood pressure provided, 59/42, occurred 4 minutes after the study drug and required significant doses of a vasoconstrictor agent for resolution. The sponsor has explained this episode on the cardiac depressant effects of thiopental, certainly a possibility given the known effects of a large thiopental bolus.

However, from the data provided, it does not seem possible to totally discount ORG 9487 as a factor in this hypotensive episode. Minor histamine release may manifest as isolated vasodilation without rash or bronchospasm. In addition, hypotension has been reported in approximately 5% of subjects who have received ORG 9487 in clinical trials. A patient with a history of poorly-controlled hypertension, as appears to be the case on examination of this patient's baseline pressures, may become profoundly hypotensive with minimal vasodilating medications. This reaction may be secondary to an up-regulation of vascular receptors or simply to a relative hypovolemia from chronically increased systemic vascular resistance. The hypotensive episode as recorded was of an extent that it could have caused myocardial ischemia/infarction, resulting in the subsequent cardiac failure on the first post-operative day. It is impossible from the data provided to discern whether this episode of cardiac failure was the primary cause of the multi-system failure leading to the patient's death.

The information provided and the conclusions that may be drawn are not sufficient to warrant a labeling change or warning. This event may be coincidental and unrelated to the administration of ORG 9487. Close post-marketing surveillance for an increased incidence of hypotensive episodes associated with the use of ORG 9487 in hypertensive patients may provide more information in this area.

**DISCONTINUATIONS:**

There were two patients in non-US studies who were discontinued due to an adverse event:

*Study 174310 (Subject 513)*

- 57 yr old male received partial dose of 1.51 mg/kg of ORG 9487; developed hypotension prior to administration of study agent and administration aborted; no relationship to ORG 9487

*Study 174313 (Subject 31)*

- 19 yr old male received 1.52 mg/kg of ORG 9487; developed bronchospasm approximately 14.5 hours after administration of the study agent; possible relationship to ORG 9487

**SERIOUS ADVERSE EVENTS:**Non-Treated Subjects – US Studies:*Study 070013 (Subject 201)*

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- 6 mo old male experienced an episode of hypoxia that resolved; patient did not receive the study drug

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- 70 yr old male received 2.56 mg/kg of ORG 9487; developed bleeding on the second post-operative day; patient recovered

*Study 174314 (Subject 5209)*

- discussed in detail in section on Deaths

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- 20 yr old female received 1.0 mg/kg of Succinylcholine; developed bleeding on the fourth post-operative day; patient recovered

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- 3 yr old female ASA 1 with no relevant medical history received 4.84 mg/kg ORG 9487 after a halothane induction for chalazion excision; patient experienced prolonged neuromuscular blockade from this initial dose; patient received two doses of reversal agents at 22 and 38 minutes after administration of ORG 9487 and was extubated; patient continued with clinical weakness, requiring 100% O<sub>2</sub> with PEEP by face mask to maintain oxygen saturation; patient received a third dose of reversal agents 54 minutes after administration of ORG 9487; the patient was considered "clinically normal" 39 minutes after the third dose of reversal agents

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- 41 yr old female with no relevant medical history received 2 mg/kg ORG 9487; reversal agents administered per protocol 2 minutes later and muscle relaxation maintained with rocuronium; reversal agents administered after rocuronium when 4 strong twitches present; clinically weak and remained intubated for approximately 5 hours after reversal agents; patient complained of some non-specific right-sided weakness the night of surgery and on the 7 day phone follow-up; neurology consult suspected underlying myopathy and scheduled work-up at a future date

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- 23 yr old female with no relevant medical history received 1.50 mg/kg ORG 9487; reversal agents administered per protocol 2 minutes later and muscle relaxation maintained with rocuronium; reversal agents administered twice after rocuronium but

no information is provided as to EMG recording at this point; patient complained of weakness, was reintubated, and was finally extubated 2 hours 47 minutes after the dose of ORG 9487; investigator suspected weakness secondary to high dose of reversal agent administered however there is no documentation of partial resolution of motor activity after either ORG 9487 or rocuronium so it is not possible to eliminate these agents as causative

### ADVERSE EVENTS:

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Respiratory	15.8	17.6	11.1
Bronchospasm	10.9	5.9	4.2
Cardiovascular	6.5	5.9	
Hypertension	2.0	5.9	
Hypotension	3.7		
General	0.8	5.9	5.6
Nervous System	0.8		1.4
Musculo-skeletal	0.3		
Skin	9.4		
Application Site	0.7	35.3	29

Upon comparison of this table with previously reported incidences for these adverse events, it is noted that, while most occur at the expected frequencies, bronchospasm in all age groups and application site reactions in infants have occurred more frequently and hypotension in adults has occurred less frequently. The following table illustrates these results.

**Table 4 Comparison of Adverse Event Incidence (%) – Present vs. Prior Data**

Adverse Event	Adults & Geriatrics		Children		Infants	
	Prior Data	Present Data	Prior Data	Present Data	Prior Data	Present Data
Bronchospasm	4	10.9	0	5.9	0	4.2
Application Site Reaction	1.4	.7	0	35.3	0.6	29
Hypotension	6.1	3.7	0.56	0	0.6	0

When the present and prior data sets are combined, bronchospasm in adults and application site reactions in infants and children continue to show a trend of increasing incidence from that reported in the prior data. The incidence of hypotension in adults, while still lower than that previously reported, is normalizing to the expected value. The following table illustrates these results.

**Table 5 Comparison of Adverse Event Incidence (%) – Pooled vs. Prior Data**

Adverse Event	Adults & Geriatrics		Children		Infants	
	Prior Data	Pooled Data	Prior Data	Pooled Data	Prior Data	Pooled Data
Bronchospasm	4	5.9	0	1	0	1.3
Application Site Reaction	1.4	1	0	3	0.6	13
Hypotension	6.1	5	0.6	0	0.56	0

From these analyses, it appears that the incidence of bronchospasm and application site reactions may be greater than originally suspected. Whether this trend is also an indication of a higher incidence of histamine related events can not be discerned at this time but bears watching in the post-marketing period. The incidence of all other adverse events as reported are consistent with previously reported data as incorporated into labeling claims.

Patricia Hartwell, MD MBA  
Medical Officer

CC: Division File  
Original NDA #20-984  
HFD-170 Patricia Hartwell, MD MBA  
HFD-170 R.A. Rappaport, MD  
HFD-170 Project Manager: Susmita Samanta

SUBJECT: NDA 20-984

NAME: Raplon™ (Rapacuronium bromide)

SPONSOR: Organon

RE: Creatine Kinase (Addendum to NDA Review)

MEDICAL OFFICER: Charles R. Cortinovis, MD MPH

DATE: 16 April, 1999

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**BACKGROUND:**

Blood chemistries were evaluated in subjects in various studies presented in the above NDA. The following comments were made by this medical officer in the Clinical Review:

"With the exception of creatine kinase (CK), the incidence of clinically significant changes in chemistry parameters did not increase as a function of increasing Org 9487 dose and did not differ in a systematic way from that observed in the placebo group. The changes in the CK are striking: the subjects who received Org 9487 exhibited a marked elevation of the CK that appeared to essentially follow a dose-response pattern. None of the placebo subjects had an elevation of the CK; 53% of the patients who received the highest dose of Org 9487 had an elevation of their creatine kinase.

*? withdrawal*

*Magnitude of ↑CK  
? weakness.*

An inquiry to the sponsor for a possible explanation of the CK values resulted in the following response March 1, 1999:

"... the subjects in Study 070011 represent 76% (19/25) of all of the cases of elevated creatine kinase. Forty percent (19/47) of the subjects in this study had clinically significant levels of creatine kinase defined as three times the upper normal level. Subjects in this study were administered doses of 1.0, 2.0, or 3.0 mg/kg of Org 9487. The subjects in Study 070011 were in general older and sicker than the average subjects in the development program, with a mean age of 60 to 64, and 60% to 75% ASA Class 3 in the three dose groups. These subjects were also undergoing a surgical procedure or had a physical condition which required the placement of an arterial cannula since the design of the study required that plasma samples for histamine be drawn from a cannula. These subjects were undergoing invasive surgeries such as thoracotomy or nephrectomy which cause a large amount of muscle trauma and therefore, would elevate creatine kinase. However, it is much more likely that the elevated creatine kinase levels observed in Study 070011 were due not to Org 9487 drug-patient interaction but to study specific effects which may have differed from other studies, such as drawing the lab specimens or type of surgery. Thirteen of the 19 subjects in Study 070011 with elevated levels of creatine kinase had surgery involving the lungs. In addition to increase in creatine kinase due to muscle trauma or myocardial infarction, high serum creatine kinase levels can

occur in patients with pulmonary infarction or pulmonary edema. When the subjects from Study 070011 are not included, there is no dose related creatine kinase response observed."

The sponsor replied (March 9, 1999 correspondence) that the composition of the placebo group in the creatine kinase study consisted of patients from study 070001.

These placebo-dosed subjects underwent the following surgical procedures:

Bilateral Inguinal herniorrhaphy	Total abdominal hysterectomy
Bilateral tubal reanastomosis	
Hysterectomy	Lumbar discectomy
Bladder neck suspension	Lumbar discectomy
Laparotomy with oophorectomy	Lumbar laminectomy
Myomectomy for uterine fibroids	Thoracic laminectomy for tumor resection
Rectocele repair	Transphenoidal hypophysectomy
Knee Arthroscopy	Bx femur
Knee Arthroscopy	Face lifting
ACL repair	Hip replacement
Knee Arthroscopy	Radical prostatectomy
Remove hardware Tibia	Total vaginal hysterectomy
Myomectomy for uterine myomas	Anterior and posterior vagino-sacro fixation on vaginal wall
Total abdominal hysterectomy	Exploratory laparotomy for abdominal mass"

#### DISCUSSION:

Additional information was received March 19, 1999. Review of this topic is now presented.

Sponsor's explanation for the elevation in the creatine kinase in the subjects who received Org 9487 is based on the following:

- Subjects were older
- Subjects were sicker (higher ASA level)
- Subjects mostly received arterial catheters
- Subjects underwent more extensive surgeries which cause a large amount of muscle trauma resulting in elevated creatine kinase.

The patients evaluated in the creatine kinase determinations came from five studies; all of the placebo patients were in one study. The time of obtaining blood samples for CK analysis relative to the time of surgery was highly variable in both Org 9487 subjects and placebo subjects. Agency requested sponsor to delineate the surgical operations of the

Org 9487 subjects and to provide statistical tests of significance for age and ASA status comparing the subjects receiving placebo and the subjects receiving Org 9487. Re-analysis of the data in addition to new information received from the sponsor lead to the following observations:

- There is no statistical difference ( $p > 0.2$ ) in age between placebo and Org 9487 subjects
- There is no statistical difference ( $p > 0.3$ ) in ASA status between placebo and all doses of Org 9487 that were administered.
- This reviewer does not agree that arterial catheters are a valid explanation for elevation of creatine kinase
- The Org 9487 subjects do appear to have undergone more extensive surgical procedures than the placebo subjects. However some of the placebo subjects did undergo operations that were of such extent that the CK should have risen above the level of significance ( $> 3$  times above normal). Also noted was one subject who did not undergo surgery but who received Org 9487 and had an elevation of the creatine kinase.
- This reviewer agrees with sponsor that if the subjects in Study 070011 are excluded than no dose-response relationship is apparent between the Org 9487 and placebo subjects.

#### CONCLUSIONS:

The methodology in the studies does not enable one to draw conclusions as to whether Org 9487 causes an elevation of creatine kinase. The patients were not stratified or randomized as to age, ASA status, or extent of surgery. The time for obtaining blood samples was not standardized.

The available information does suggest that there may be an association between rapacuronium bromide and significant elevation of the creatine kinase. This association is particularly relevant to this new molecular entity because muscle relaxants of similar molecular structure are known to cause skeletal muscle myopathies during prolonged infusion. If skeletal muscle myopathy were to occur after rapacuronium bromide administration, the creatine kinase would be expected to rise above normal. The data presented in the clinical trials does not enable this reviewer to form conclusions on the cause or effect of the elevated CK levels observed in the Raplon™ subjects.

#### RECOMMENDATIONS:

1. Raplon™ should not be approved for  
is proved to be safe.
2. Pharmacovigilance Division should be consulted to monitor this agent for the occurrence of myopathy.

C. Cortinovis

Charles R. Cortinovis, MD MPH  
Medical Officer

Comments on Independent Review

Noted that CK's in study 070-011 were obtained on the average of 24 h p op. Procedures, no dissections were in all cases, long and involved muscle manipulation finding more likely a few of trauma surgery & sampling time rather than primary muscle damage related to drug. No reports of muscle weakness (p reversal of blockade) or EMG Δ's to suggest myopathy. I disagree with Dr. Cortinovis' assessment, but concur that "myopathy" may be something to watch for in future as sponsor explores more chronic dosing paradigms.

IS/  
7/29/99