CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20984

CHEMISTRY REVIEW(S)

DIVISION OF ANESTHETICS, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS, HFD-170

Review of Chemistry, Manufacturing and Controls

NDA #: 20-984 DATE REVIEWED: 3/31/99

REVIEW: # 4

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	24-06-98	25-06-98	02-07-98
AMENDMENT	22-06-99	23-06-99	13-07-99

NAME & ADDRESS OF APPLICANT: ORGANON, INC.
375 Mount Pleasant Avenue
West Orange, New Jersey, 07092

DRUG PRODUCT:
Proprietary: Raplon(rapacuronium bromide) for Injection

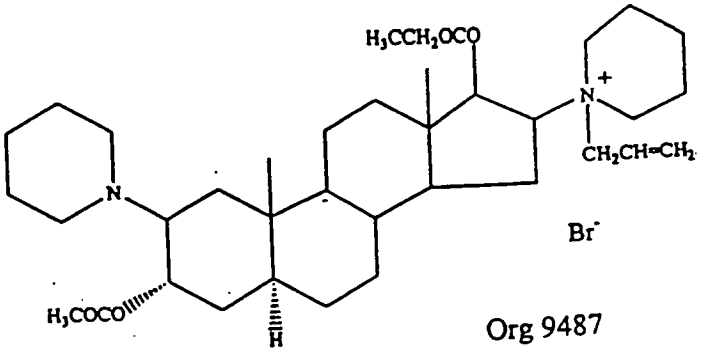
Established: Rapacuronium Bromide
Code Name/#: Org 9487
Chem.Type/Ther.Class:

PHARMACOL. CATEGORY/INDICATION: Non-depolarizing Neuromuscular Blocking Agent

DOSAGE FORM: Injection
STRENGTHS: 100 MG/vial and 200 MG/vial
ROUTE OF ADMINISTRATION: Intravenous and Intramuscular
DISPENSED: Rx X

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1-[3α-(Acetyloxy)-17β-(1-oxopropoxy)-2β-(1-piperidinyl)-5α-androstan-16β-yl]-1-(2-propenyl)piperidinium bromide.



Org 9487

Molecular formula : $C_{37}H_{61}BrN_2O_4$.

Relative molecular mass : 677.78.

COMMENTS:

The applicant was sent an approvable letter dated April 22, 1999 which indicated that before approval certain deficiencies had to be corrected. The chemist made the following request:

Revise the specifications for the drug product to read % for ORG 9488 and no more than % for total impurities.

FDA's Reason:

After reviewing the 24 month's stability data for the four batches of the Raplon Injection shown below (See Table), it was recommended that the firm reduce the specification limits for the metabolite ORG 9488 from % to % and the total degradation products from % and store the product at refrigerated temperature (2-8 degrees centigrade) because the stability data showed an increase in these limits at room temperature and better results at refrigerated temperatures.

We were also concerned about the safety of the patient, if he/she received the Raplon Injection after being stored at room temperature with such high impurity limits.

Stability Data Reviewed:

***Hypersil ODS** Method all of the stability lots for ORG 9487 for Injection:*

Lot OA.03.96/B-6A- 200 mg/vial
Lot OA.03.96/B-6B -100 mg/vial
Lot OA.03.96/B-7A- 200 mg/vial
Lot OA.03.96/B-7B-100 mg/vial
Lot OA.09.96/B-8A- 200 mg/vial
Lot OA.09.96/B-8B- 100 mg/vial

Hypersil Method for:

Lot OA.03.96/B-6A- 200 mg/vial
Lot OA.09.96/B-8B- 100 mg/vial

Zorbax Method for:

Lot OA.03.96/B-6B -100 mg/vial
Lot OA.03.96/B-7A- 200 mg/vial
Lot OA.03.96/B-7B-100 mg/vial
Lot OA.09.96/B-8A- 200 mg/vial

MAXIMUM AMOUNT OF TOTAL I-9488 METABOLITE AND TOTAL IMPURITY OBSERVED AT THE END OF 24 MONTHS STABILITY STUDY

Batches	Container/Closure	5 °C Total Degradation (%)	25°C/60%RH Products (%)	I –9488 Metabolite 5°C (%)	I-9488 Metabolite 25°C /60%RH (%)
6 A	Stopper	1.0	2.3	0.5	1.4
6 B	Stopper	1.3	4.4	0.8	3.6
7A	Stopper	1.0	3.1	0.6	2.4
7B	Stopper	1.0	3.3	0.6	2.4
8A	Stopper	0.8	2.5	0.7	2.0
8B	Stopper	1.1	5.6	1.0	5.1

FIRM'S RESPONSE:

Organon did not agree with our recommendation and indicated and indicated that their specification limits of % for ORG 9488 and % for total impurities is supported by actual stability data under room temperature storage conditions of 25°C/60%RH and that these limits are strongly supported by clinical data involving specific trials conducted with ORG 9488
Organon showed where ORG 9488 was administered at levels significantly higher than a patient would be exposed to during administration of Raplon for Injection with the proposed specifications.

Organon submitted the following clinical data:

The proposed specifications for Raplon™ for Injection allow for a total of % total degradation products which include up to % Org 9488. Org 9488 was administered to patients in two clinical studies. In Study 174206, a bolus dose of 0.2 mg/kg Org 9488 was administered to patients, and in Study 174207, patients received a slow infusion of Org 9488 (0.1 to 0.15 mg/kg/min) for 3 to 7 minutes.

Table 1 presents the doses of Org 9488 administered in these two clinical studies expressed as mg/kg. In addition, this table presents the amount of Org 9488 that would

be administered to a patient at the proposed specification of % in the doses of Raplon™ studied in our clinical program.

TABLE 1

	Org 9488
Study 174206 (n=7)	0.2 mg/kg
Study 174207 (n=7)	0.68 mg/kg*
Proposed Specification of %	
at 1.5 mg/kg Raplon	0.068 mg/kg
at 2.5 mg/kg Raplon	0.113 mg/kg

*adapted from page 41 of the clinical report for study 174207

As can be seen from the data presented, the mean amount of Org 9488 administered to patients in Studies 174206 and 174207 were approximately 2 to 10 times the amount of Org 9488 which would be administered to patients receiving Raplon™ for Injection at either a dose of 1.5 mg/kg or 2.5 mg/kg with the proposed specification of % for Org 9488.

In Study 174206, no neuromuscular block was observed in 3 of the 7 subjects administered Org 9488 and the maximum block ranged from % in the other 4 subjects. Org 9488 provided only a minimal amount of neuromuscular block.

In Study 174207, a slow infusion of Org 9488 (0.1 - 0.15 mg/kg/min) was administered to 7 subjects with the goal of the study being to achieve a 95% block of neuromuscular function. The infusion was administered over 3 to 7 minutes and the mean clinical duration of this dose of Org 9488 was 57 minutes.

Cardiovascular changes observed in the Org 9488 studies were similar to subjects receiving Raplon™ in other studies. During the 5 minutes after administration of Org 9488, the mean blood pressure decreased and the mean heart rate increased. No drug related adverse events were reported due to Org 9488. In Study 174206, one subject undergoing surgery for mouth and neck carcinoma had a Serious Adverse Event. The subject had respiratory insufficiency after extubation in the ICU the day following surgery. The subject was reintubated and recovered. One subject in Study 174207 had an adverse event of post-operative bleeding. These events were not considered to be drug related.

Organon claims with the above clinical trials demonstrated that ORG 9488 can be safely administered directly to patients and levels 2 to 10 times the proposed specifications of % for ORG 9488 and there is no need to store the product a refrigerated temperatures as recommended by FDA.

FDA's RESPONSE:
The reviewing chemist and the chemistry team leader, Dr. D'Sa then decided to consult with the other reviewers, namely the pharmacologist, the pharmakineticist, and medical officer to get their opinion on how they felt about the patients receiving such amount of ORG 9488 and total degradation products when administered the Raplon for Injection. See Attached consults.

In addition, the reviewing chemist reviewed the stability data of 12 months at 30°C/60%RH to see if the data fell within the firm's suggested specification limits:

I-9488 and TOTAL DEGRADATION PRODUCT AT THE END OF 12 MONTHS AT 30°C

Batches	Container/Closure	I-9488 Metabolite 30°C/75%RH (%)	30°C/75%RH Total Degradation Products (%)
6 A	Stopper	1.4	< 2.6
6 B	Stopper	3.3	< 4.4
7A	Stopper	2.0	< 3.0
7B	Stopper	2.7	< 3.7
8A	Stopper	1.3	< 2.1
8B	Stopper	3.2	< 3.8

The data at this temperature is within the firm's specification limits at twelve months. However, based on all of the submitted stability data we have only allowed an 18 months expiration date for the product.

The following pages contain the stability protocol and the actual testing that is performed. and The structures involved

TABLE B

Storage Condition	Initial	MONTHS							
		3	6	9	12	18	24	36	48
5°C ± 3°C		*	*	*	*	*	*	*	*
25°C/60% RH	*	*	*	*	*	*	*	*	*
30°C/40% RH		*	*	*	*	*	*	*	*
30°C/60% RH			*		*				
30°C/75% RH		*	*	*	*	*	*	*	*
40°C/75% RH		*	*						

* Indicates samples will be removed from stability cabinet/incubator for assay analysis.

TABLE C

TESTS	TEST METHODS	SAMPLE SIZE	STATIONS TO BE TESTED
Appearance - Cake [β]			
Assay			
Related Foreign Steroids			
Use Dilution Test:[*] a. Assay b. pH c. Tonicity d. Related Foreign Steroids			
Constituted Solution [β] a. Completeness of solution b. Clarity (Ph. Eur.) c. Particulate Matter - Visual d. Color (Ph. Eur.)			
Identification			
Moisture Content [β]			
Particulate Matter: HIAC			
pH			
Bacterial Endotoxin [β]			
Sterility			
Content and Weight Variation [β]			
Uniformity of Mass			

* Test to be performed upon reconstitution (day 1) and after 24 hours (day 2).

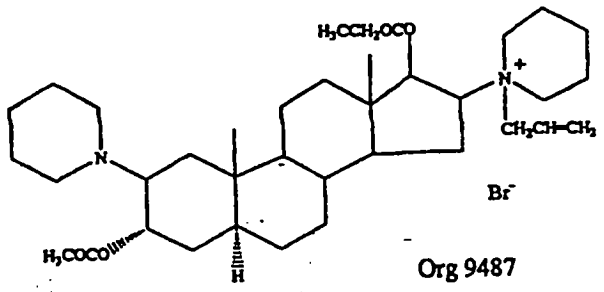
β Use appearance samples to perform test.

α Use constituted solution samples to perform test.

β Samples will be tested individually, not as a composite.

[A] Use 10 additional sample weights from Content and Weight Variation Test for a total of 20 weights.

[3α-(Acetyloxy)-17β-(1-oxopropoxy)-2β--piperidinyl)-5α-androstan-16β-yl]-1--propenyl)piperidinium bromide.



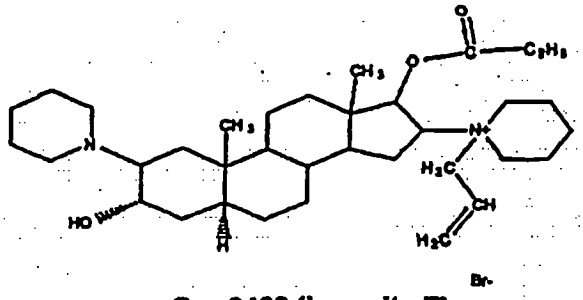
Org 9487

Molecular formula : $C_{37}H_{61}BrN_2O_4$.

Relative molecular mass : 677.78.

Metabolism

Rapacuronium bromide undergoes hydrolysis of the acetyloxy-ester bond at the 3-position to form the major and active metabolite, Org 9488 (3-hydroxy metabolite). Relative to its parent, Org 9488 has more potency and slower onset of action. This hydrolysis is non-specific and can occur at physiological temperature and pH. This hydrolysis may also be catalyzed by esterases of unknown identity and at unknown sites. It appears as if cytochrome P450 enzyme system is not involved in the hydrolysis of rapacuronium bromide. In addition to the major metabolite Org 9488, it appears from the mass balance study that there may be seven additional minor metabolites of unknown identity.



Org 9488 (Impurity F)

Impurity F(Org 9488) : 1-[(2B,3a,5a,16B,17B)-3-hydroxy-17-(oxypropoxy)-2-(1-piperidinyl) androstan-16-yl]-1-(2-propenyl) piperidiniuim bromide

CONCLUSION:

Based on the pharmacologist consult review and PK consult review, concurred by the medical officer, it appears that the specification for the major metabolite and total impurities of % and % respectively are acceptable from a safety perspective. In order to relax the specification for the expiration dating of 18 months and storage between 2-25°C, evidence is provided that the impurity specification of 5% is within the limits under stability studies conducted at 2°C, 25°C, and 30°C. The proposal for relaxing this specification is therefore acceptable. The storage statement: " Store between 2-25°C" is also acceptable.

/S/ 7/27/99

Juanita Ross, M.S.
Review Chemist

/S/ 7/27/99

Albinus D Sa, Ph.D.,
Chemist Team Leader

CBM 7/30/99

CC:
Orig. NDA 20-984
HFD-170/ Div File
HFD-170/Jross
HFD-170/Cotinovis
HFD-170/Samanthas
HFD-820/GibbsJ
Filename: 20984.doc

DIVISION OF ANESTHETICS, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS, HFD-170

Review of Chemistry, Manufacturing and Controls

NDA #: 20-984 **Review #** 3 **DATE REVIEWED:** 4/12/99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	4/09/99	(Facsimile dated 4/09/99)	

NAME & ADDRESS OF APPLICANT: ORGANON, INC.
375 Mount Pleasant Avenue
West Orange, New Jersey, 07092

DRUG PRODUCT:

Proprietary: Raplon (rapacuronium bromide) for Injection

Established: Rapacuronium Bromide

Code Name/#: Org 9487

Chem.Type/Ther.Class:

PHARMACOL. CATEGORY/INDICATION: Non-depolarizing Neuromuscular Blocking Agent

DOSAGE FORM: Lyophilized cake For Injection

STRENGTHS: 100 mg/vial and 200 mg/vial

ROUTE OF ADMINISTRATION: Intravenous and Intramuscular

DISPENSED: Rx X

Remarks:

This review is performed by Albinus D'Sa because Juanita Ross, the primary reviewer has reported sick today. The review mainly deals with the applicant's response to three issues that were raised previously in a fax dated April 8, 1999 by the agency.

1) The applicant has agreed to include an optical rotation test for release for the drug substance. The test is being developed and the specification should be ready this week.

Comment: The proposal is acceptable.

2) The applicant has proposed a room temperature storage of 25 degrees C. with an expiration date of 18 months for the product. The new total impurity limit proposed is %. However, the data indicates that the applicant is able to reproducibly maintain a stable product with % total impurity for 24 months at 2-8 degrees C. The impurity, I-9488, which is also the active metabolite, is the single most prominent impurity. It is present in the range of %. With a single outlier of %.

DIVISION OF ANESTHETICS, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS, HFD-170

Review of Chemistry, Manufacturing and Controls

NDA #: 20-984 **DATE REVIEWED:** April 6,1999

Review: 2 **Reviewer:** Juanita Ross

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	05-04-99	06-04-99	

NAME & ADDRESS OF APPLICANT: ORGANON, INC.
375 Mount Pleasant Avenue
West Orange, New Jersey, 07092

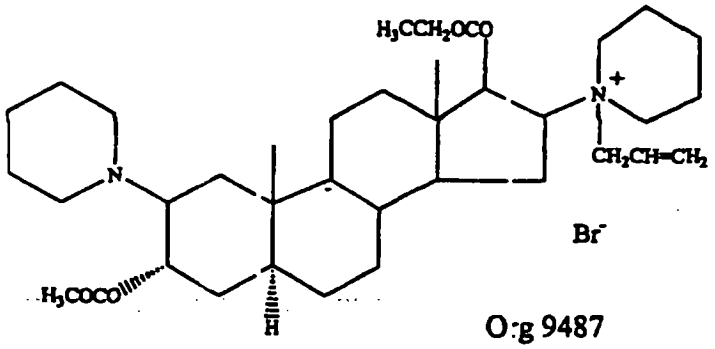
DRUG PRODUCT:
Proprietary: Raplon(rapacuronium bromide) for Injection

Established: Rapacuronium Bromide
Code Name/#: Org 9487
Chem.Type/Ther.Class:

PHARMACOL. CATEGORY/INDICATION: Non-depolarizing Neuromuscular Blocking Agent

DOSAGE FORM: Injection
STRENGTHS: 100 MG/vial and 200 MG/vial
ROUTE OF ADMINISTRATION: Intravenous and Intramuscular
DISPENSED: Rx X

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Org 9487

: $C_{37}H_{61}BrN_2O_4$.

: 677.78.

1-[3α-(Acetyloxy)-17β-(1-oxopropoxy)-2β-(1-piperidinyl)-5α-androstan-16β-yl]-1-(2-propenyl)piperidinium bromide.

Comment: Based on the data provided, and based on the fact that the drug product used in clinical trials was refrigerated, the drug product should be stored in a refrigerator at 2-8 degrees C (36-46 degrees F). The total impurity specification should be no more than % and the spec for I-9488 should be no more than at %

3) The applicant's response to question on the preparation of the reference standard is acceptable

Comment: The essence of the response is that a fully characterized regular production batch , with an assay value of 100% would serve as a reference standard. This is acceptable.

Conclusions and Recommendations:

The Establishment Inspections Report is still being awaited from the field, therefore Office of Compliance is unable to provide a recommendation. Bruce Hartman of the Office of Compliance has been contacted and is going to provide a recommendation shortly by E-mail and through the EES. Pending this report, the application is approvable from the CMC standpoint. However, in the letter to applicant the following should be noted:

Based on the data provided, and based on the fact that the drug product used in clinical trials was refrigerated, the drug product should be stored in a refrigerator at 2-8 degrees C (36-46 degrees F). The total impurity specification should be no more than % and the spec for I-9488 should be no more than at %

Once again, a note to the project manager: please add the standard methods validation paragraph in the letter.

/S/ 4/12/99

Albinus D'Sa, Ph.D.
Chemistry Team Leader

CC:

Orig.NDA 20-984
HFD-170/ Division File ? DFS
HFD-170/ Chemists/ JRoss/AD'Sa
HFD-170/PM/ SSamanta
HFD-820/Jgibbs/SKoeppky

DIVISION OF ANESTHETICS, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS, HFD-170

Review of Chemistry, Manufacturing and Controls

NDA #: 20-984

DATE REVIEWED: 3/31/99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	24-06-98	25-06-98	02-07-98
AMENDMENT	01-09-98	02-09-98	02-12-98
AMENDMENT	15-09-98	16-09-98	
AMENDMENT	24-09-98	25-09-98	13-10-98

NAME & ADDRESS OF APPLICANT: ORGANON, INC.
375 Mount Pleasant Avenue
West Orange, New Jersey, 07092

DRUG PRODUCT:

Proprietary: Raplon(rapacuronium bromide) for Injection

Established: Rapacuronium Bromide

Code Name/#: Org 9487

Chem.Type/Ther.Class:

PHARMACOL. CATEGORY/INDICATION: Non-depolarizing Neuromuscular Blocking Agent

DOSAGE FORM: Injection

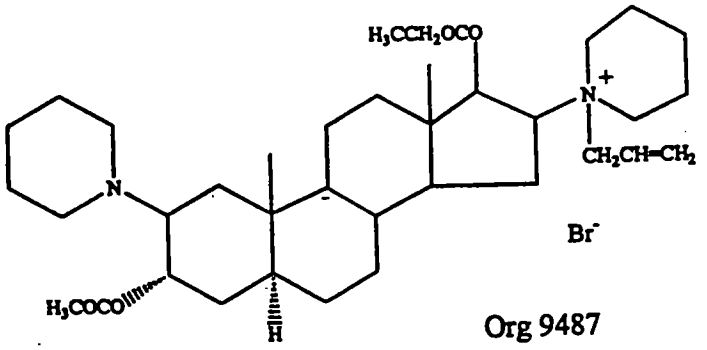
STRENGTHS: 100 MG/vial and 200 MG/vial

ROUTE OF ADMINISTRATION: Intravenous and Intramuscular

DISPENSED: **Rx** X

CHEMICAL NAME, STRUCTURAL FORMULA,

1-[3α-(Acetyloxy)-17β-(1-oxopropoxy)-2β-(1-piperidinyl)-5α-androstan-16β-yl]-1-(2-propenyl)piperidinium bromide.



Org 9487

Molecular formula : $C_{37}H_{61}BrN_2O_4$.

Relative molecular mass : 677.78.

SUPPORTING DOCUMENTS:

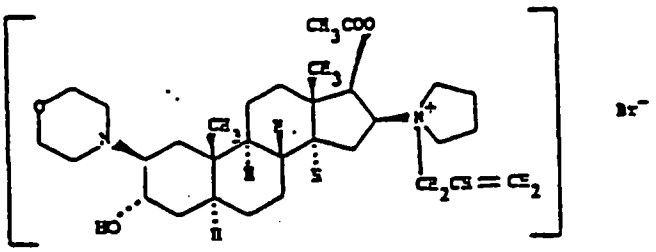
Type of Document Number	Subject of Document	Document Holder	Address
IND	IND	Organon Inc.	Organon Inc. 375 Mt. Pleasant Ave West Orange, NJ 07052
DMF	Drug Substance		
DMF	Facilities and Procedures		
DMF	Facilities and Procedures		
DMF	Facilities and Procedures	Organon Inc.	Organon Inc. 375 Mt. Pleasant Avenue *West Orange. NJ 07052*
DMF	Packaging Materials		
DMF	Packaging Material		
DMF	Packaging Materials		

RELATED DOCUMENTS:

NDA 20-214 (Rocuronium Bromide),
NDA 18-776 (Vecuronium Bromide)
NDA 17-015 (Pancuronium Bromide)
NDA 19-638 (Pipecuronium Bromide)

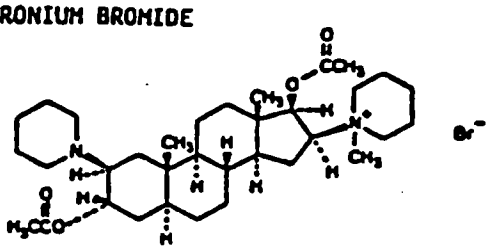
RELATED STRUCTURES

(3a.)

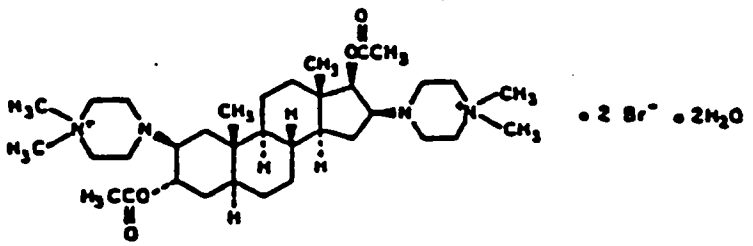


ROCURONIUM BROMIDE

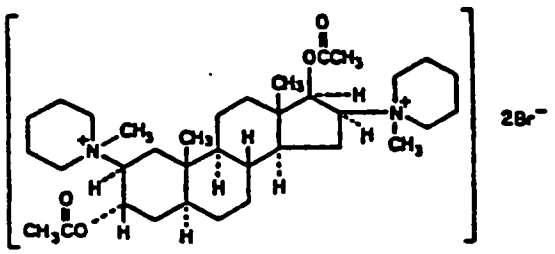
VECURONIUM BROMIDE



PIPECURONIUM BROMIDE

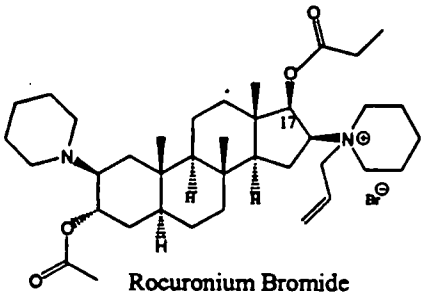


PANCURONIUM BROMIDE

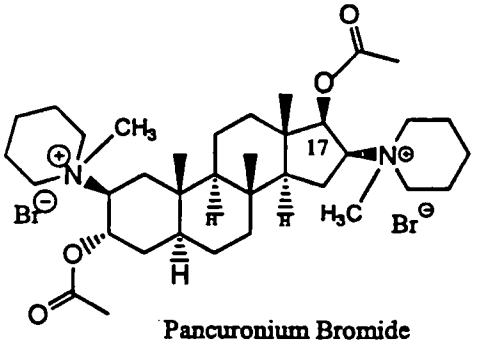


COMMENTS:

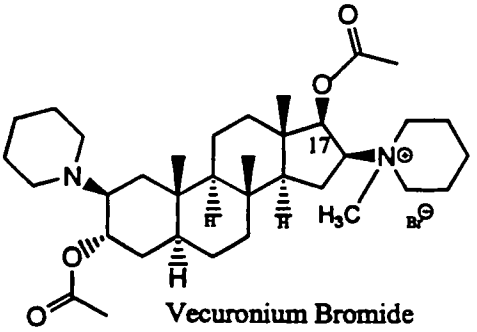
Raplon ™ (rapacuranium bromide) is chemically designated as a synthetic steroid molecule with a mono-quaternary ammonium structure . This chemical structure has a basic steroid framework similar to other neuromuscular blocking agents like vecuronium, pancuronium, rocuronium, and pipecuronium. Rapacuranium is closest in its chemical structure to vecuronium and pancuronium. It differs from vecuronium at the quaternary ammonium site and at the 17-hydroxy ester. Pancuronium is the di-quaternary ammonium salt of vecuronium. Rapacuranium, is thus distinguished as being a propenyl bromide ammonium salt with a 17-propionate hydroxy ester that has the same basic steroid backbone as the rest of the family of steroid molecules.



Rocuronium Bromide
Chemical formula: $C_{37}H_{61}BrN_2O_4$
Molecular Weight: 667.79



Pancuronium Bromide



Vecuronium Bromide

The drug product is supplied as a sterile lyophilized cake in strengths of 100 mg/ 5 mL vial and 200 mg /10 mL vial. However, when either of these vials are appropriately reconstituted with bacteriostatic water to a volume of 5 mL and 10 mL, respectively, the product obtained contains 20 mg per mL of rapacuronium bromide as a sterile isotonic solution.. The lyophilized cake contains the following inactive ingredients: citric acid anhydrous, mannitol, sodium phosphate buffer, and either sodium hydroxide or phosphoric acid to buffer to adjust the pH. Each of the reconstituted solutions are isotonic and have a pH of 4. It should be noted that the solution is not preserved and therefore is meant for single use only.

The CMC review of the drug substance noted that the drug substance, a white to off white powder is fairly unstable and needs to be stored under refrigeration and protected from light and moisture. The

specifications have the usual test for the establishing identity, purity and quality. A maximum total impurity limit of % and a spec for moisture of % have been instituted. The applicant was asked to show that impurity M, which is the isomeric mono-quaternary ammonium salt, where the propenyl group is on the 2-(1-piperdine) ring could easily be distinguished from the drug substance. By synthesizing the molecule the applicant has demonstrated that the two salts have different retention times and that impurity M only occurs in very small amounts ($\leq 0.1\%$) in the drug substance. Even though this is a single enantiomer, there is no spec for optical rotation of enantiomeric purity. Telecon dated 3/31/99 asked the applicant address the issue. The drug substance is not very hygroscopic and before the drug is formulated in to the drug product, it will be tested for identity, assay, moisture and microbial limits.

The drug substance is manufactured at The release testing is performed at and it is transported to Organon Inc., West Orange, NJ. Here the drug substance is re-tested before formulation into the drug product. The vials are then transported to Organon Inc, Allentown, PA, where the product is inspected, secondary packaged and labeled. Telecon dated 3/31/99 and 4/1/99 asked the applicant to clearly indicate the role of each of these facilities.

The drug product is a sterile lyophilized cake, marketed as a "for injection" dosage form. There are two package sizes, i.e., 100 mg/vial and 200 mg/vial. It is packaged in USP glass vials with gray butyl siliconized stoppers and aluminum flip-off seals. The two potencies are obtained from a single bulk solution, which contains 66.67 mg/mL of the active ingredient. Volumes of 1.5 mL and 3.0 mL were used to prepare the 100 mg/vial and the 200 mg/vial packaged product, respectively.

The drug product has the appropriate specs for identity, assay, purity, and quality. The applicant was asked in telecon dated 4/1/99, to tighten the impurity specs based on the data submitted. The current specs for total degradation products are 3.0% at release and 6.0% at stability. The applicant had 12 months long term stability from 5° C to 30 °C/ with relative humidity ranging from 40% to 75% RH, data on 4 lots of the drug product. Based on the data an 18-month expiration date is recommended for the product.

Microbiology was consulted to HFD-160. Comments from the first review dated October 19, 1998 requested the applicant to provide several items pertaining to the sterile validation process. The applicant's response is currently being reviewed. Complete & Satisfactory as of 4/6/99 Com

Method Validation package is currently being prepared to be evaluated by the appropriate FDA laboratories. A standard co-operation paragraph should be included in the approval letter. Inspections of two of the four facilities are incomplete. Office of compliance was asked for a status report on 4/1/99.

CONCLUSIONS AND RECOMMENDATIONS:

From the Chemistry Manufacturing and Controls standpoint this application is approvable pending a satisfactory response by the applicant to telecons dated 3/31/99 and 4/1/99, a satisfactory microbiology review, and an acceptable inspection report from the office of compliance. Method Validation package is currently being prepared to be evaluated by the appropriate FDA laboratories. A standard co-operation paragraph should be included in the approval letter.

/S/ 4/1/99

Juanita Ross, Review Chemist

/S/ 4/1/99

Albinus D'Sa, Ph.D. Chemist Team Leader

CC
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HFD-170/Medical Officer/CortinovisC
HFD-170/ CSO/SamanthaS
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