

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74945

ADMINISTRATIVE DOCUMENTS

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 74-945

Date of Submission: May 21, 1997

Applicant's Name: **Marsam Pharmaceuticals Inc.**

Established Name: **Atracurium Besylate Injection 10 mg/mL, 10 mL Multiple Dose Vial**

Labeling Deficiencies:

1. CONTAINER - 10 mL Multiple Dose Vial

Satisfactory in final print.

2. CARTON - 10s x 10 mL Multiple Dose Vial

Satisfactory in final print.

3. INSERT

- a. PRECAUTIONS

Long-Term Use in Intensive Care Unit (ICU)

Paragraph 1, sentence 2 - ... of atracurium besylate during ...

- b. DOSAGE AND ADMINISTRATION

Add the following text after the **Use by Continuous Infusion - Infusion in the Operating Room (OR)** subsection:

Infusion in the Intensive Care Unit (ICU): The principles for infusion of atracurium in the OR are also applicable to use in the ICU.

An infusion rate of 11 to 13 mcg/kg/min (range 4.5 to 29.5) should provide adequate neuromuscular block in adult patients in an ICU. Limited information suggests that infusion rates required for pediatric patients in the ICU may be higher than in adult patients. There may be wide interpatient variability in dosage requirements and these requirements may increase or decrease with time (see PRECAUTIONS: Long-Term Use in

Intensive Care Unit [ICU]). Following recovery from neuromuscular block, readministration of a bolus dose may be necessary to quickly re-establish neuromuscular block prior to reinstatement of the infusion.

Please revise your insert labeling as instructed above, and submit final printed insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP Z3		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in NOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	

Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?	X		
Labeling(continued)	Yes	No	N.A.
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opespray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T % and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			X
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

FOR THE RECORD: (portions carried forth from first review)

- MODEL LABELING/PATENTS & EXCLUSIVITY:** A unique situation - The RLD; Tracrium®; Burroughs Wellcome Co.; had two supplements approved within a week of each other:

NDA 18-831/SLR-018 AP 01-JUN-94; Revised June 1993
/SE5-019 AP 06-JUN-94; Revised May 1994

The review was based on the 6-6-94 approval with two exceptions where the 6-1-94 labeling was used - one pertaining to the exclusivity (PRECAUTIONS section), the

other a Use in the Elderly subsection in the CLINICAL PHARMACOLOGY and PRECAUTIONS sections.

I-108, Exclusivity for Expanded Use For ICU Patients Undergoing Long-Term Infusion During Mechanical Ventilation, expired on June 6, 1997.

The patent for the drug substance expired 12/18/96.

2. INACTIVE INGREDIENTS - See p. 100 of first submission for C & C statement.
3. STORAGE RECOMMENDATIONS
Both NDA and the ANDAs are the same: Refrigerate at 2° to 8° C (36° to 46° F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25° C/77° F), use within 14 days even if rerefrigerated.
4. PACKAGING CONFIGURATIONS
Both ANDA & RLD have the same product line:
10 mg/mL, preserved, 10 mL multiple dose vials x 10s
10 mg/mL, unpreserved, 5 mL single dose vials x 10s
5. BIOEQUIVALENCE - Waiver request - Waiver granted 12-16-96.
6. Marsam is the sole manufacturer. See pp. 192 and 196 of the first submission.
7. LABEL and LABELING COMMENTS
 - a. SHARED INSERT - This ANDA shares an insert with Marsam's single dose (5 mL - no benzyl alcohol) atracurium formulation, ANDA 74-944.
 - b. The draft container label and carton depict the warning in a box and both text and box are in red print. This is acceptable. (The RLD does not do this.)
 - c. Marsam has been pro-active in its labeling of neuromuscular blocking agents in response to comments they've received from physicians and pharmacists to distinguish these products. They have added the statement "WARNING: PARALYZING AGENT" to their container labels. See discussion on p. 72, vol 1.1. They first did this with their Vecuronium. (See below.) In concurrence with John Grace, we will allow it since it was acceptable for their vecuronium. The RLD does not have this statement, however. The statement was not added to their carton.

Marsam is a distributor of Vecuronium for Steris. Steris submitted an SSCBE with Marsam's labels as their

model (ANDA 74-334/SL-001). The labels contained the above addition. This was consulted to HFD-170 and found acceptable. The Division endorsed the change and further recommended that the Warning informing of "respiratory depression" be revised to read "respiratory arrest" to be more precise. The Division intends to notify sponsors of neuromuscular agents to revise. It will be some time before the changes are formally approved, I am told by Dr. Landow, Medical Officer.

- d. VIAL SEAL - Marsam also imprints the "WARNING: PARALYZING AGENT" statement on its vial seals. It is white print on a red seal with a clear plastic flip-off cap so the warning is visible. This is mentioned on p. 72 with a reference to see section XIV. A similar cap was also part of their Vecuronium ANDA's recent SSCBE. This is labeling but it wasn't submitted with the rest of their labels and labeling. Marsam submitted 2 actual seals/caps (unbroken units) in an envelope following page 117 of the 2-24-97 piece. Per reviewer Carol Holquist, two were accepted before for final print for her CISplatin applications.
- e. The specified pH range is different than the innovator's. This was acceptable to the chemist. See Notes to the Chemist (with reply) in first labeling review.
- f. The firm chooses to employ different NDC numbers on the container vs the carton. See pp. 73 and 75 in vol 2.1.
- g. A "Discard by:" statement is present for stability/potency purposes to note when vial removed from refrigeration, not for antimicrobial growth issues.
- h. AUXILIARY DRUG STICKER - Marsam submitted draft drug stickers. The RLD uses them, but the office drug folder doesn't have an RLD sample and am unsure if it is actual "approved" labeling. I have not been successful in my attempts to obtain it. To date, we have never commented on it in any atracurium application. The sticker is red with black print "ATRACURIUM BESYLATE _____ mg/mL", and intended for use on the outside of admixtures. No comments have been made. We have reviewed other ANDAs which did submit them and we haven't commented. We also have not commented when an ANDA did not submit them.
- i. PRODUCT DIFFERENTIATION - Marsam differentiates its single dose vial from its multiple dose vial. The characteristic Marsam expression of strength triangle on the single dose vial is white print on a teal

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: **74-945** Date of Submission: February 24, 1997

Applicant's Name: **Marsam Pharmaceuticals Inc.**

Established Name: **Atracurium Besylate Injection 10 mg/mL, 10 mL Multiple
Dose Vial**

Labeling Deficiencies:

1. GENERAL COMMENT

 Please note and acknowledge: Exclusivity for Expanded Use For ICU Patients Undergoing Long-Term Infusion During Mechanical Ventilation expires on June 6, 1997. If your application is going to be approved after that date, you will be asked to revise your insert labeling prior to approval to include reference to this indication.

2. VIAL SEAL AND FLIP-OFF CAP

 Satisfactory in final print.

3. CONTAINER - 10 mL Multiple Dose Vial

 Satisfactory in draft.

4. CARTON - 10s x 10 mL Multiple Dose Vial

 Satisfactory in draft.

5. INSERT

 a. CLINICAL PHARMACOLOGY

 i. Paragraph 2 - ... monitored to assess degree of ...

 ii. Paragraph 3, sentence 2 - ... with increasing atracurium doses.

b. WARNINGS

Last paragraph - Revise to read:

... alcohol. BENZYL ALCOHOL HAS BEEN ASSOCIATED WITH ... COMPLICATIONS IN NEWBORN INFANTS WHICH ARE SOMETIMES FATAL. Atracurium ... single dose vials ...

c. PRECAUTIONS

i. Long-Term Use in Intensive Care Unit (ICU)

A). Paragraph 2, sentence 1 - ... levels or clinical ... ["or" rather than "and"]

B). Line 6 - "cerebral edema" [two words]

ii. Labor and Delivery, paragraph 2, line 5 - ... and atracurium besylate dose should ...

iii. Close the gap between the Pediatric Use and the Use in the Elderly subsections.

d. OVERDOSAGE

Paragraph 1, sentence 1 - ... experience with atracurium besylate overdose.

e. DOSAGE AND ADMINISTRATION

i. Bolus Doses for Intubation and Maintenance of Neuromuscular Block

A). Adults, paragraph 3, sentence 1 - Delete the terminal zero, i.e., 0.08 to 0.1 mg/kg ...

B). Children and Infants - Delete paragraph 2.

C). Special Considerations, paragraph 3, sentence 3 - ... prior to atracurium administration.

ii. Use by Continuous Infusion, Infusion in the Operating Room (OR) - Combine paragraphs 1 and 2.

Please revise your insert labeling as instructed above, and submit final printed container labels and carton and insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

~~Jerry Phillips~~
~~Director~~
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