CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74944

ADMINISTRATIVE DOCUMENTS

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

ANDA Number: 74-944 Date of Submission: February 24, 1997

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

Established Name: **Atracurium Besylate Injection 10 mg/mL, 5 mL Single 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 - 5 mL Single Dose Vial

   Side Panel - Since room permits, allow "rerefrigerated" to appear on one line.

4. CARTON - 10s x 5 mL Single 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 overdosage.

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 container label and 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
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

RECORD OF TELEPHONE CONVERSATION

I spoke with Ms. Kompa regarding chemistry deficiency and comments from the field chemist.

1) The field chemist validating the method could not complete the calculations of the method since it lacked the following details: which one of the two methods is used for atracurium calculations, and how is rrt calculated. There was no formula provided for the quantitation of impurities. The method states that only the largest of the unspecified impurities should be reported. This statement should be revised to include all impurities. The firm will revise the method / answer all the concerns and will fax an amendment. I will forward it to Nick and Daniel Frost at Phil. Labs.

2) The second topic discussed was the response received from Marsam on May 23, 1997 for the minor amendment. Marsam was informed that the word 'unspecified impurity' is non-existent and they can qualify the impurity at rrt only as a unknown (in which case a stability limit of % is the maximum) or as known (a larger % may be allowed). Marsam was also advised that a PF proposal is available for Atrcurium (drug substance and product) and they should be prepared to follow as soon as it becomes official. I further requested Jill to provide chromatograms of Benzene sulphonic acid and benzyl alcohol under atracurium chromatographic conditions and levels so that the possibility of impurities in excipients can be eliminated. She was also advised that they have to provide a commitment to investigate further the impurity at rrt

DATE
7-16-97

ANDA NUMBERS
74-944 and 74-945

PRODUCT NAME
Atracurium Besylate Injection, Preserved and Non-Preserved

FIRM NAME
Marsam Pharmaceuticals

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

Jill Kompa

TELEPHONE NUMBER

609-489-5330

SIGNATURE

/S/

Radhika Rajagopalan,
Chemistry Reviewer

7/16/97

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

ANDA Number: **74-944** Date of Submission: May 21, 1997

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

Established Name: **Atracurium Besylate Injection 10 mg/mL, 5 mL Single Dose Vial**

Labeling Deficiencies:

1. CONTAINER - 5 mL Single Dose Vial

   The 10 mg/mL in the triangle appears on the label as the most prominent expression of strength - not the total contents as is the practice with single dose vials. The 50 mg/5 mL is not prominent - someone may assume that the total contents are 10 mg and not 50 mg. Please revise so that 50 mg appears in the triangle.

2. CARTON - 10s x 5 mL Single Dose Vial

   See comment under CONTAINER.

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 reinstitution of the infusion.

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.

_____

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 23		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	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			
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	

Labeling(continued)	Yes	No	N.A.
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 HOW 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	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			
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	
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, Opaspray?			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 1/2 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:

1. 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 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 granted 12-16-96.

6. Marsam is the sole manufacturer. See pp. 188, 192.

7. LABEL and LABELING COMMENTS

   a. SHARED INSERT - This ANDA shares an insert with Marsam's benzyl alcohol preserved atracurium formulation in multiple dose vials, ANDA 74-945.

   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. 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 . 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 p. 73.

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 background. The multiple dose is black print on white background with a teal border.

j. The container label does not have an "Each mL" statement secondary to space constraints. The RLD does not have one either. The space is used for the respiratory depression Warning. We have allowed this for other ANDAs.

k. John Grace indicated the statement NOT FOR USE IN NEWBORNS (see WARNINGS) should be deleted from the DESCRIPTION and HOW SUPPLIED sections. It is not permitted in the regs and should be most prominent where it rightly goes - in the WARNINGS section. Marsam indicated they would include it per their side-by-side. Comment was made to request deletion. This was done, but one other site was overlooked where the RLD also doesn't use it - DOSAGE AND ADMINISTRATION, Bolus Doses for Intubation and Maintenance of Neuromuscular Block, Children and Infants, Paragraph 2. Deletion requested.

l. EXCLUSIVITY - The firm added the information concerning the ICU long term use of this drug product to the PRECAUTIONS section with this submission but they failed to add it to the DOSAGE AND ADMINISTRATION section. This review asks them to do this.

Date of Review: 7-1-97 Date of Submission: 5-21-97

Primary Reviewer: Adolph Vezza Date: 7/1/97

Team Leader: John Grace Date: 7/8/97

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

ANDA Number: **74-944** Date of Submission: August 21, 1996

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

Established Name: **Atracurium Besylate Injection 10 mg/mL, 5 mL Single Dose Vial**

Labeling Deficiencies:

1. VIAL SEAL AND FLIP-OFF CAP

   Satisfactory in draft.

2. CONTAINER - 5 mL Single Dose Vial

   a. Add the statement "Discard Unused Portion."

   b. Please assure the word "**REFRIGERATE**" appears prominently. The innovator uses red print to draw attention to this important storage requirement.

   c. Include the place of business in the "Manufactured By" statement. [See 21 CFR 201.1(a)]

3. CARTON - 10s x 5 mL Single Dose Vial

   a. See comments a and b under CONTAINER.

   b. Revise the statement beginning "For indications, dosage, precautions, etc., ..." to read "Usual Dosage: See enclosed package insert."

   c. Each mL statement - Include the active ingredient and the pH range.

   d. Storage Recommendation - Include the statement "Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use within 14 days even if rerefrigerated."

4. INSERT

   Revisions are indicated in the enclosed "mock-up" of your proposed draft labeling. Additional comments follow.

a. GENERAL COMMENT

We acknowledge your comments regarding placement of the statement "NOT FOR USE IN NEWBORNS (See WARNINGS)" with respect to benzyl alcohol in the DESCRIPTION and HOW SUPPLIED sections. This important information is most prominent in the WARNINGS section per 21 CFR 201.57(e). Delete this statement from the DESCRIPTION and HOW SUPPLIED sections.

b. DESCRIPTION

Revise the chemical name to read as it appears in the insert labeling of the reference listed drug or as the second name that appears in the USAN monograph.

c. PRECAUTIONS

Insert the "Long-Term Use in Intensive Care Unit (ICU)" subsection that appears in the labeling of the listed drug (Tracrium®; Burroughs Wellcome Co.; Revised June 1993; Approved June 6, 1994) to appear as the second subsection. However, revise the first paragraph only to read as it appears in the listed drug's June 1, 1994, approved labeling:

When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular block must be considered. There is only limited information available on the efficacy and safety of long-term (days to weeks) intravenous atracurium infusion to facilitate mechanical ventilation in the ICU. These data suggest that there is wide interpatient variability in dosage requirements and that these requirements may decrease or increase with time.

d. ADVERSE REACTIONS

Add the following text as the last paragraph in this section:

There have been rare spontaneous reports of seizures in ICU patients following long-term infusion of atracurium to support mechanical ventilation. There are insufficient data to define the contribution, if any, of atracurium and/or its metabolite laudanosine. (See PRECAUTIONS, Long-Term Use in Intensive Care Unit [ICU]).

e. DOSAGE AND ADMINISTRATION

i. Revise paragraph 3 to read:

The use of a peripheral nerve stimulator to monitor muscle twitch suppression and recovery will permit the most advantageous use of atracurium and minimize the possibility of overdosage.

ii. Relocate paragraph 4 to be the last paragraph in the Dosage and Administration section.

Please revise your container labels and carton and insert labeling as instructed above, and submit draft labels and labeling and final printed vial seals and flip-off caps.

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