

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74944

APPROVAL LETTER

JUL 28 1998

Marsam Pharmaceuticals Inc.
Attention: Steven W. Brown
Building 31, 24 Olney Avenue
P.O. Box 1022
Cherry Hill, NJ 08034
|||||

Dear Sir:

This is in reference to your abbreviated new drug application dated August 21, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Atracurium Besylate Injection, 10 mg/mL, (preservative-free).

Reference is also made to your amendments dated March 30, and June 22, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Atracurium Besylate Injection, 10 mg/mL (preservative-free) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Tracrium® Injection, 10 mg/mL (preservative-free) of Glaxo Wellcome Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/s/

7/22/98

Douglas L. Sporn

Director

Office of Generic Drugs

Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74944

DRAFT FINAL PRINTED LABELING

INDICATIONS AND USAGE

Atracurium Besylate Injection is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS

Atracurium besylate is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS

ATRACURIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINERGIC REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE.

DO NOT GIVE ATRACURIUM BESYLATE BY INTRAMUSCULAR ADMINISTRATION.

Atracurium has no known effect on consciousness, pain threshold, or sensation. It should be used only with adequate anesthesia. Atracurium Besylate Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, atracurium may be inactivated and a free acid may be precipitated.

Atracurium Besylate Injection 10 mL multiple dose vials contain benzyl alcohol. **BENZYL ALCOHOL HAS BEEN ASSOCIATED WITH AN INCREASED INCIDENCE OF NEUROLOGICAL AND OTHER COMPLICATIONS IN NEWBORN INFANTS WHICH ARE SOMETIMES FATAL.** Atracurium Besylate Injection 5 mL single dose vials do not contain benzyl alcohol.

PRECAUTIONS

General

Although atracurium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering atracurium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial atracurium besylate dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since atracurium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with atracurium than with other muscle relaxants.

Atracurium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular block in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis.

Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which atracurium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, atracurium did not trigger this syndrome.

Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn.

The safety of atracurium has not been established in patients with bronchial asthma.

Long-Term Use in Intensive Care Unit (ICU)

When there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular block must be considered. The long-term (1 to 10 days) infusion of atracurium besylate during mechanical ventilation in the ICU has been evaluated in several studies. Average infusion rates of 11 to 13 mcg/kg/min (range: 4.5 to 29.5) were required to achieve adequate neuromuscular block. These data suggest that there is wide interpatient variability in dosage requirements. In addition, these studies have shown that dosage requirements may decrease or increase with time. Following discontinuation of infusion of atracurium in these ICU studies, spontaneous recovery of four twitches in a train-of-four occurred in an average of approximately 30 minutes (range: 15 to 75 min) and spontaneous recovery to a train-of-four ratio >75% (the ratio of the height of the fourth to the first twitch in a train-of-four) occurred in an average of approximately 60 minutes (range: 32 to 108 min).

Little information is available on the plasma levels or clinical consequences of atracurium metabolites that may accumulate during days to weeks of atracurium administration in ICU patients. Laudanosine, a major biologically active metabolite of atracurium without neuromuscular blocking activity, produces transient hypotension and, in higher doses, cerebral excitatory effects (generalized muscle twitching and seizures) when administered to several species of animals. There have been rare spontaneous reports of seizures in ICU patients who have received atracurium or other agents. These patients usually had predisposing causes (such as head trauma, cerebral edema, hypoxic encephalopathy, viral encephalitis, uremia). There are insufficient data to determine whether or not laudanosine contributes to seizures in ICU patients.

WHENEVER THE USE OF ATRACURIUM OR ANY NEUROMUSCULAR BLOCKING AGENT IS CONTEMPLATED IN THE ICU, IT IS RECOMMENDED THAT NEUROMUSCULAR TRANSMISSION BE MONITORED CONTINUOUSLY DURING ADMINISTRATION WITH THE HELP OF A NERVE STIMULATOR. ADDITIONAL DOSES OF ATRACURIUM OR ANY OTHER NEUROMUSCULAR BLOCKING AGENT SHOULD NOT BE GIVEN BEFORE THERE IS A DEFINITE RESPONSE TO T, OR TO THE FIRST TWITCH, IF NO RESPONSE IS ELICITED, INFUSION ADMINISTRATION SHOULD BE DISCONTINUED UNTIL A RESPONSE RETURNS.

Hemofiltration has a minimal effect on plasma levels of atracurium and its metabolites, including laudanosine. The effects of hemodialysis and hemoperfusion on plasma levels of atracurium and its metabolites are unknown.

Drug Interactions

Drugs which may enhance the neuromuscular blocking action of atracurium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quindine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonistic effect should be considered.

The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular block induced by atracurium. Atracurium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular block.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and fertility studies have not been performed. Atracurium was evaluated in a battery of three short-term mutagenicity tests. It was non-mutagenic in both the Ames Salmonella assay at concentrations up to 1000 mcg/plate, and in a rat bone marrow cytogenetic assay up to paralyzing doses. A positive response was observed in the mouse lymphoma assay under conditions (80 and 100 mcg/mL, in the absence of metabolic activation) which killed over 80% of the treated cells; there was no mutagenicity at 60 mcg/mL and lower concentrations which killed up to half of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations (1200 mcg/mL and higher) which also killed over 80% of the treated cells.

Mutagenicity testing is intended to simulate chronic (years to lifetime) exposure in an effort to determine potential carcinogenicity. Thus, a single positive mutagenicity response for a drug used infrequently and/or briefly is of questionable clinical relevance.

Pregnancy: Teratogenic Effects: Pregnancy Category C

Atracurium has been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Atracurium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Atracurium was administered subcutaneously on days 6 through 18 of gestation to non-ventilated Dutch rabbits. Treatment groups were given either 0.15 mg/kg once daily or 0.10 mg/kg twice daily. Lethal respiratory distress occurred in two 0.15 mg/kg animals and in one 0.10 mg/kg animal, with transient respiratory distress or other evidence of neuromuscular block occurring in 10 of 19 and in 4 of 20 of the 0.15 mg/kg and 0.10 mg/kg animals, respectively. There was an increased incidence of certain spontaneously occurring visceral and skeletal anomalies or variations in one or both treated groups when compared to non-treated controls. The percentage of male fetuses was lower (41% vs. 51%) and the post-implantation losses were increased (15% vs. 8%) in the group given 0.15 mg/kg once daily when compared to the controls; the mean numbers of implants (6.5 vs. 4.4) and normal live fetuses (5.4 vs. 3.8) were greater in this group when compared to the control group.

Labor and Delivery

It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Atracurium besylate (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to atracurium in any of the newborn infants, although small amounts of atracurium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular block may be unsatisfactory and the atracurium besylate dose should be lowered as indicated.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when atracurium besylate is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 1 month have not been established.

Use in the Elderly

Since marketing in 1983, uncontrolled clinical experience and limited data from controlled trials have not identified differences in effectiveness, safety, or dosage requirements between healthy elderly and younger patients (see CLINICAL PHARMACOLOGY); however, as with other neuromuscular blocking agents, the use of a peripheral nerve stimulator to monitor neuromuscular function is suggested (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Observed in Controlled Clinical Studies

Atracurium was well tolerated and produced few adverse reactions during extensive clinical trials. Most adverse reactions were suggestive of histamine release. In studies including 875 patients, atracurium was discontinued in only one patient (who required treatment for bronchial secretions), and six other patients required treatment for adverse reactions attributable to atracurium (wheezing in one, hypotension in five). Of the five patients who required treatment for hypotension, three had a history of significant cardiovascular disease. The overall incidence rate for clinically important adverse reactions, therefore, was 7/875 or 0.8%. The table below includes all adverse reactions reported attributable to atracurium during clinical trials with 875 patients.

Adverse Reaction	PERCENT OF PATIENTS REPORTING ADVERSE REACTIONS			Total (n=875)
	Initial Atracurium Besylate Dose (mg/kg)			
	0.00-0.30 (n=485)	0.31-0.50* (n=366)	≥ 0.60 (n=24)	
Skin Flush	1.0%	8.7%	29.2%	5.0%
Erythema	0.6%	0.5%	0%	0.6%
Itching	0.4%	0%	0%	0.2%
Wheezing/Bronchial Secretions	0.2%	0.3%	0%	0.2%
Hives	0.2%	0%	0%	0.1%

*Includes the recommended initial dosage range for most patients.

Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. The table below summarizes the incidences of substantial vital sign changes noted during atracurium clinical trials with 530 patients, without cardiovascular disease, in whom these parameters were assessed.

Vital Sign Change	PERCENT OF PATIENTS SHOWING ≥30% VITAL SIGN CHANGES			Total (n=530)
	FOLLOWING ADMINISTRATION OF ATRACURIUM			
	Initial Atracurium Besylate Dose (mg/kg)			
	0.00-0.30 (n=365)	0.31-0.50* (n=144)	≥ 0.60 (n=21)	
Mean Arterial Pressure				
Increase	1.9%	2.8%	0%	2.1%
Decrease	1.1%	2.1%	14.3%	1.9%
Heart Rate				
Increase	1.6%	2.8%	4.8%	2.1%
Decrease	0.8%	0%	0%	0.6%

*Includes the recommended initial dosage range for most patients.

Observed in Clinical Practice

Based on initial clinical practice experience in approximately 3 million patients who received atracurium in the U.S. and in the United Kingdom, spontaneously reported adverse reactions were uncommon (approximately 0.01% to 0.02%). The following adverse reactions are among the most frequently reported, but there are insufficient data to support an estimate of their incidence:

General: Allergic reactions (anaphylactic or anaphylactoid responses) which, in rare instances, were severe (e.g., cardiac arrest)

Musculoskeletal: Inadequate block, prolonged block

Cardiovascular: Hypotension, vasodilatation (flushing), tachycardia, bradycardia

Respiratory: Dyspnea, bronchospasm, laryngospasm

Integumentary: Rash, urticaria, reaction at injection site

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]).

OVERDOSAGE

There has been limited experience with atracurium besylate overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation. Excessive doses of atracurium can be expected to produce enhanced pharmacological effects. Overdosage may increase the risk of histamine release and cardiovascular effects, especially hypotension. If cardiovascular support is necessary, this should include proper positioning, fluid administration, and the use of vasopressor agents if necessary. The patient's airway should be assured, with manual or mechanical ventilation maintained as necessary. A longer duration of neuromuscular block may result from overdosage and a peripheral nerve stimulator should be used to monitor recovery. Recovery may be facilitated by administration of an anticholinesterase reversing agent such as neostigmine, edrophonium, or pyridostigmine, in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. The appropriate package inserts should be consulted for prescribing information.

Three pediatric patients (3 weeks, 4 and 5 months of age) unintentionally received doses of 0.8 mg/kg to 1 mg/kg of atracurium besylate. The time to 25% recovery (50 to 55 minutes) following these doses, which were 5 to 6 times the ED₅₀ dose, was moderately longer than the corresponding time observed following doses 2 to 2.5 times the atracurium ED₅₀ dose in infants (22 to 36 minutes). Cardiovascular changes were minimal. Nonetheless the possibility of cardiovascular changes must be considered in the case of overdose.

An adult patient (17 years of age) unintentionally received an initial dose of 1.3 mg/kg of atracurium besylate. The time from injection to 25% recovery (83 minutes) was approximately twice that observed following maximum recommended doses in adults (35 to 45 minutes). The patient experienced moderate hemodynamic changes (13% increase in mean arterial pressure and 27% increase in heart rate) which persisted for 40 minutes and did not require treatment.

The intravenous LD₅₀'s determined in non-ventilated male and female albino mice and male Wistar rats were 1.9, 2.01 and 1.31 mg/kg, respectively. Deaths occurred within 2 minutes and were caused by respiratory paralysis. The subcutaneous LD₅₀ determined in non-ventilated male Wistar rats was 262.8 mg/kg. Tremors, ptosis, loss of reflexes and respiratory failure preceded death which occurred 45 to 120 minutes after injection.

DOSAGE AND ADMINISTRATION

To avoid distress to the patient, atracurium should not be administered before unconsciousness has been induced. Atracurium should not be mixed in the same syringe, or administered simultaneously through the same needle, with alkaline solutions (e.g., barbiturate solutions).

Atracurium besylate should be administered intravenously. DO NOT GIVE ATRACURIUM BESYLATE BY INTRAMUSCULAR ADMINISTRATION. Intramuscular administration of atracurium may result in tissue irritation and there are no clinical data to support this route of administration.

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.

Bolus Doses for Intubation and Maintenance of Neuromuscular Block

Adults: An atracurium besylate dose of 0.4 to 0.5 mg/kg (1.7 to 2.2 times the ED₅₀), given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular block achieved approximately 3 to 5 minutes after injection. Clinically required neuromuscular block generally lasts 20 to 35 minutes under balanced anesthesia. Under balanced anesthesia, recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

Atracurium is potentiated by isoflurane or enflurane anesthesia. The same initial atracurium besylate dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if atracurium is first administered under steady state of isoflurane or enflurane, the initial atracurium besylate dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg, to adjust for the potentiating effects of these anesthetic agents. With halothane, which has only a marginal (approximately 20%) potentiating effect on atracurium, smaller dosage reductions may be considered.

Atracurium besylate doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular block during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial atracurium besylate injection, but the need for maintenance doses should be determined by clinical criteria. Because atracurium lacks cumulative effects, maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane. Higher atracurium doses (up to 0.2 mg/kg) permit maintenance dosing at longer intervals.

Children and Infants: No atracurium dosage adjustments are required for pediatric patients two years of age or older. An atracurium dose of 0.3 to 0.4 mg/kg is recommended as the initial dose for infants (1 month to 2 years of age) under halothane anesthesia. Maintenance doses may be required with slightly greater frequency in infants and children than in adults.

Special Considerations: An initial atracurium besylate dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for adults, children, or infants with significant cardiovascular disease and for adults, children, or infants with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular block or difficulties with reversal have been demonstrated. There has been no clinical experience with atracurium in these patients, and no specific dosage adjustments can be recommended. No atracurium dosage adjustments are required for patients with renal disease.

An initial atracurium besylate dose of 0.3 to 0.4 mg/kg is recommended for adults following the use of succinylcholine for intubation under balanced anesthesia. Further reductions may be desirable with the use of potent inhalation anesthetics. The patient should be permitted to recover from the effects of succinylcholine prior to atracurium administration. Insufficient data are available for recommendation of a specific initial atracurium besylate dose for administration following the use of succinylcholine in children and infants.

Use by Continuous Infusion

Infusion in the Operating Room (OR): After administration of a recommended initial bolus dose of Atracurium Besylate Injection (0.3 to 0.5 mg/kg), a diluted solution of atracurium besylate can be administered by continuous infusion to adults and children aged 2 or more years for maintenance of neuromuscular block during extended surgical procedures. Infusion of atracurium should be individualized for each patient. The rate of administration should be adjusted according to the patient's response as determined by peripheral nerve stimulation. Accurate dosing is best achieved using a precision infusion device.

Infusion of atracurium should be initiated only after early evidence of spontaneous recovery from the bolus dose. An initial infusion rate of 9 to 10 mcg/kg/min may be required to rapidly counteract the spontaneous recovery of neuromuscular function. Thereafter, a rate of 5 to 9 mcg/kg/min should be adequate to maintain continuous neuromuscular block in the range of 89 to 99% in most pediatric and adult patients under balanced anesthesia. Occasional patients may require infusion rates as low as 2 mcg/kg/min or as high as 15 mcg/kg/min.

The neuromuscular blocking effect of atracurium administered by infusion is potentiated by enflurane or isoflurane and, to a lesser extent, by halothane. Reduction in the infusion rate of atracurium should, therefore, be considered for patients receiving inhalation anesthesia. The rate of atracurium besylate infusion should be reduced by approximately one-third in the presence of steady-state enflurane or isoflurane anesthesia; smaller reductions should be considered in the presence of halothane.

In patients undergoing cardiopulmonary bypass with induced hypothermia, the rate of infusion of atracurium required to maintain adequate surgical relaxation during hypothermia (25° to 28°C) has been shown to be approximately half the rate required during normothermia.

Spontaneous recovery from neuromuscular block following discontinuation of atracurium infusion may be expected to proceed at a rate comparable to that following administration of a single bolus dose.

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.

Infusion Rate Tables: The amount of infusion solution required per minute will depend upon the concentration of atracurium in the infusion solution, the desired dose of atracurium, and the patient's weight. The following tables provide guidelines for delivery, in mL/hr (equivalent to microdrops/min when 60 microdrops = 1 mL), of atracurium solutions in concentrations of 0.2 mg/mL (20 mg in 100 mL) or 0.5 mg/mL (50 mg in 100 mL) with an infusion pump or a gravity flow device.

Patient Weight (Kg)	Atracurium Besylate Infusion Rates for a Concentration of 0.2 mg/mL									
	Drug Delivery Rate (mcg/kg/min)									
	5	6	7	8	9	10	11	12	13	
	Infusion Delivery Rate (mL/hr)									
30	45	54	63	72	81	90	99	108	117	
35	53	63	74	84	95	105	116	126	137	
40	60	72	84	96	108	120	132	144	156	
45	68	81	95	108	122	135	149	162	176	
50	75	90	105	120	135	150	165	180	195	
55	83	99	116	132	149	165	182	198	215	
60	90	108	126	144	162	180	198	216	234	
65	98	117	137	156	176	195	215	234	254	
70	105	126	147	168	189	210	231	252	273	
75	113	135	158	180	203	225	248	270	293	
80	120	144	168	192	216	240	264	288	312	
90	135	162	189	216	243	270	297	324	351	
100	150	180	210	240	270	300	330	360	390	

Patient Weight (Kg)	Atracurium Besylate Infusion Rates for a Concentration of 0.5 mg/mL									
	Drug Delivery Rate (mcg/kg/min)									
	5	6	7	8	9	10	11	12	13	
	Infusion Delivery Rate (mL/hr)									
30	18	22	25	29	32	36	40	43	47	
35	21	25	29	34	38	42	46	50	55	
40	24	29	34	38	43	48	53	58	62	
45	27	32	38	43	49	54	59	65	70	
50	30	36	42	48	54	60	66	72	78	
55	33	40	46	53	59	66	73	79	86	
60	36	43	50	58	65	72	79	86	94	
65	39	47	55	62	70	78	85	94	101	
70	42	50	59	67	76	84	92	101	109	
75	45	54	63	72	81	90	99	108	117	
80	48	58	67	77	86	96	106	115	125	
90	54	65	76	86	97	108	119	130	140	
100	60	72	84	96	108	120	132	144	156	

Compatibility and Admixtures

Atracurium besylate infusion solutions may be prepared by admixing Atracurium Besylate Injection with an appropriate diluent such as 5% Dextrose Injection USP, 0.9% Sodium Chloride Injection USP, or 5% Dextrose and 0.9% Sodium Chloride Injection USP. Infusion solutions should be used within 24 hours of preparation. Unused solutions should be discarded. Solutions containing 0.2 mg/mL or 0.5 mg/mL atracurium besylate in the above diluents may be stored either under refrigeration or at room temperature for 24 hours without significant loss of potency. Care should be taken during admixture to prevent inadvertent contamination. Visually inspect prior to administration.

Spontaneous degradation of atracurium besylate has been demonstrated to occur more rapidly in lactated Ringer's solution than in 0.9% sodium chloride solution. Therefore, it is recommended that Lactated Ringer's Injection USP not be used as a diluent in preparing solutions of Atracurium Besylate Injection for infusion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Atracurium Besylate Injection, 10 mg/mL, is available as the following:
 NDC 0209-0460-22-5 mL, single dose vials, packaged in 10s.
 NDC 0209-0462-22-10 mL, multiple-dose vials, packaged in 10s. Contains benzyl alcohol (see WARNINGS).

Storage

Atracurium Besylate Injection should be refrigerated at 2°-8°C (36°-46°F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use Atracurium Besylate Injection within 14 days even if refrigerated.
CAUTION: Federal (USA) law prohibits dispensing without prescription.

Marsam Pharmaceuticals Inc.
 Cherry Hill, NJ 08034

Issued 7-97

C0460

NDC 0209-0460-22
1 Tray • 5 mL
10 Single Dose Vials

50
mg

ATRACURIUM
Besylate Injection

50 mg/5 mL
(10 mg/mL)

REFRIGERATE

MARSAM
PHARMACEUTICALS, INC.
Cherry Hill, NJ 08034

WARNING: Atracurium besylate is a potent drug which may cause respiratory depression. Facilities must be immediately available for artificial respiration.

For Intravenous Injection: Sterile, non-pyrogenic.

Usual Dosage: See enclosed package insert.
Each mL contains 10 mg atracurium besylate, benzenesulfonic acid (added to adjust pH to 3.2 to 3.7), and Water for Injection.

REFRIGERATE: Store at 2° to 8°C (36° to 46°F). DO NOT FREEZE.
Discard Unused Portion.

Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use within 14 days even if refrigerated.

CAUTION: Federal law prohibits dispensing without prescription.

B0460



N

MARSAM
PHARMACEUTICALS, INC.
Cherry Hill, NJ 08034

REFRIGERATE
(10 mg/mL)
50 mg/5 mL

ATRACURIUM
Besylate Injection

NDC 0209-0460-22
1 Tray • 5 mL
10 Single Dose Vials

50
mg

28

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74944

CHEMISTRY REVIEW(S)

DIVISION REVIEW SUMMARY

ANDA #: 74-944 **DRUG PRODUCT:** Atracurium Besylate Injection,
Unpreserved

FIRM: Marsam Pharmaceuticals Inc.

DOSAGE: Injection

STRENGTH: 10 mg/mL, 5 mL vials

cGMP STATEMENT/EIR UPDATE STATUS:

cGMP: GMP Certification is enclosed. (Pages 189-191).

EER: Pending.

BIO STUDY(ies)/BIOEQUIVALENCE STATUS:

On 12/23/96 the Division of Bioequivalence issued a no comments letter to the firm.

METHODS VALIDATION (Including dosage form description):

The methods were verified by Philadelphia field laboratories for drug substance and product. The methods are found adequate after incorporation of the comments from the Field labs.

STABILITY(Conditions, Containers, methods):

Bio batch

Evaluation of stability indicating methods:

Stability Assays

Test	Specifications
Appearance	Clear, colorless liquid.
Assay (active)	%
Particulate matter	
pH	

Degradation products	
Total	NMT %
Cp 7110 trans	NMT %
Laudanosine	NMT %
Unknown/unspecified	NMT %
7113	NMT %
7114	NMT %
7115 + 7116	NMT %
7110 cis	NMT %
CP 7185	NMT %
CP 7149	NMT %
Unidentified RRT 0.11	NMT %
Sterility	Complies
Bacterial Endotoxin	EU/MG

Stability studies were done on the bio batch. Containers are the same those listed in the container section. Stability studies are in conformance with the FDA Guidelines.

LABELING REVIEW STATUS: Satisfactory dated 7/31/97.

STERILIZATION VALIDATION (If Applicable): Acceptable (dated June 10, 1997).

BATCH SIZES:

BIO BATCH: Lot # M96020 (L size)

NDS source:

STABILITY BATCHES (different from BIO BATCH, manuf. site, process)

Stability batch is the same as the bio-batch

PROPOSED PRODUCTION BATCH

L is the proposed production batch size.

Process is the same as the demonstration batch.

COMMENTS: Approvable

CHEMISTRY REVIEWER:

Radhika Rajagopalan

DATE:

April 7, 1998

Reviewer is on extended leave; letter needs to issue
(Signature) 7/8/98

1. CHEMISTRY REVIEW NO. 5
2. ANDA # 74-944
3. NAME AND ADDRESS OF APPLICANT
Marsam Pharmaceuticals Inc.
Attention: Steven W. Brown R.Ph.
Building 31, 24 Olney Avenue
Cherry Hill, NJ 08034
4. LEGAL BASIS FOR SUBMISSION
US Patent No. 4,179,507 for the listed drug will expire on December 18, 1996. Exclusivity I-108 (Expanded Use - For ICU patients undergoing long-term infusion during mechanical ventilation) expired on June 6, 1997.
5. SUPPLEMENT
N/A
6. PROPRIETARY NAME
N/A
7. NONPROPRIETARY NAME
Atracurium Besylate
8. SUPPLEMENT PROVIDE FOR:
N/A
9. AMENDMENTS AND OTHER DATES:

August 21, 1996--	ANDA Original Submission.
September 20, 1996--	FDA acknowledgment letter.
December 23, 1996--	Division of Bioequivalence issued Bio acceptance letter
January 27, 1997--	FDA major deficiency letter (chemistry, micro and labeling)
February 24, 1997--	ANDA amendment by firm
May 8, 1997--	FDA Minor deficiency letter by fax (chemistry, micro and labeling)
May 21, 1997--	ANDA minor amendment by firm
May 23, 1997--	New correspondence by firm
June 10, 1997--	Micro review acceptable
July 1, 1997--	Labeling review #3 deficient
July 16, 1997--	T-conference initiated by chemist
July 18, 1997--	Amendment by firm (chemistry issues)
July 23, 1997	Amendment by firm
September 22, 1997--	Not approvable letter by FDA
February 5, 1998--	Minor amendment by firm
March 2, 1998--	Minor deficiencies to firm (review #4)

March 30, 1998--

Amendment by firm

10. PHARMACOLOGICAL CATEGORY
Neuromuscular Blocking Agent
11. Rx or OTC
Rx
12. RELATED DMF #
13. DOSAGE FORM
Injectable, IV
single dose
14. POTENCY
10 mg/mL; 5 mL
(Unpreserved)
15. CHEMICAL NAME AND STRUCTURE
2,2-(pentamethylenebis(oxycaronylethylene))bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium) dibenzenesulfonate
16. RECORDS AND REPORTS
N/A
17. COMMENTS
Awaiting satisfactory EER.
Final acceptable label review satisfactory (7/30/97).
Minor amendment (3/30/98) addresses all the deficiencies from the method verification. The firm has also updated drug substance specifications as per USP PF Monograph. Administrative review on this application is already completed. Hence, ANDA can be approved.
Bio waiver granted on 12/23/96.
18. CONCLUSIONS AND RECOMMENDATIONS
Chemistry is approved.
19. REVIEWER:
Radhika Rajagopalan, Ph.D.
- DATE COMPLETED:
4/7/98

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
74944

MICROBIOLOGY REVIEW

OFFICE OF GENERIC DRUGS, HFD-640
Microbiologists Review #1
October 15, 1996

A. 1. ANDA 74-944

APPLICANT Marsam Pharmaceuticals, Inc

2. PRODUCT NAMES: Atracurium Besylate Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:

10 mg/mL, 5 mL Single Dose glass vial, Intravenous

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Skeletal muscle relaxant
(neuromuscular block)

B. 1. DATE OF INITIAL SUBMISSION: August 21, 1996

(Received August 22, 1996)

2. DATE OF AMENDMENT: None

3. RELATED DOCUMENTS: DMF

DMF

DMF

4. ASSIGNED FOR REVIEW: 10/8/96

C. REMARKS The subject drug is into 5 mL
vials on the filling line 303, Room 15 of the
Cherry Hill NJ pharmaceutical manufacturing
facility.

D. CONCLUSIONS: The submission is not recommended for
approval on the basis of sterility assurance.
The specific comments regarding the
process are provided in

IS/
Andrea S. High, Ph. D. 10/15/96

cc: Original ANDA
Duplicate ANDA
Division Copy
Field Copy

Drafted by A. High, HFD 640 x:wp\microrev\74-944

Initialed by F. Fang or F. Holcombe, Jr. 10/17/96

OFFICE OF GENERIC DRUGS, HFD-640
Microbiologists Review #3
June 9, 1997

- A. 1. ANDA 74-944
- APPLICANT Marsam Pharmaceuticals, Inc
2. PRODUCT NAMES: Atracurium Besylate Injection
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
10 mg/mL, 5 mL Single Dose glass vial, Intravenous
4. METHOD(S) OF STERILIZATION:
5. PHARMACOLOGICAL CATEGORY: Skeletal muscle relaxant
(neuromuscular block)
- B. 1. DATE OF INITIAL SUBMISSION: August 21, 1996
(Received August 22, 1996)
2. DATE OF AMENDMENT: May 21, 1997
Subject of This Review (Received May 22, 1997)
3. RELATED DOCUMENTS: None
4. ASSIGNED FOR REVIEW: 6/9/97
- C. REMARKS The subject amendment provides for the response to the microbiology deficiencies in the letter dated May 8, 1997. The amendment also provides for a change in the closure sterilization cycles.
- D. CONCLUSIONS: The submission is recommended for approval on the basis of sterility assurance. The specific comments regarding the process are provided

JSI 6/10/97
Andrea S. High, Ph. D.

cc: Original ANDA
Duplicate ANDA
Division Copy
Field Copy

Drafted by A. High, HFD 640 x:wp\microrev\74-944a.2
Initialed by F. Fang or F. Holcombe, Jr.

6/17/97

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
74944

BIOEQUIVALENCY REVIEW(S)

DEC 16 1996

Atracurium Besylate Injection
10 mg/mL, 5 mL Single-dose Vial
ANDA #74-944
Reviewer: Moheb H. Makary
WP 74944W.896

Marsam Pharmaceuticals, Inc.
Cherry Hill, NJ
Submission Date:
August 21, 1996

Review of a Waiver Request

I. Objective:

The firm requested a waiver of bioequivalence study requirements for its product Atracurium Besylate Injection, 10 mg/mL, 5 mL vial. Innovator product is Tracrium® Injection 10 mg/mL, 5 mL (single-dose vials) and 10 mL (multiple-dose vials) manufactured by Glaxo Wellcome.

Atracurium Besylate is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation. It should be administered intravenously.

II. Formulations:

The formulations of the proposed test product and reference product are shown below:

	Reference Product	Proposed Test Products
	Tracrium® Injection 10 mg/mL 5 mL Vial	Atracurium Besylate Injection 10 mg/mL 5 mg Vial
Atracurium Besylate	10 mg/mL	10 mg/mL
Benzenesulfonic Acid	To adjust pH	qs To adjust pH
Water for Injection	qs	qs

III. Comments:

1. As shown above, the proposed test product, Atracurium Besylate Injection, 10 mg/mL, 5 mL single-dose vial contains the same active and inactive ingredients in the same quantities per mL as the reference product, Tracrium® Injection, 10 mg/mL, 5 mL Vial.

2. The test product is a solution intended for intravenous administration.

3. Waiver of in vivo bioequivalence study requirements may be granted based on 21 CFR 320.22 (b) (1).

IV. Recommendation:

The Division of Bioequivalence agrees that the information

submitted by Marsam Pharmaceuticals Inc., demonstrates that Atracurium Besylate Injection 10 mg/mL, 5 mL Vial, falls under Section 320.22 (b) (1) of Bioavailability/Bioequivalence Regulations. Waiver of in vivo bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation, Atracurium Besylate Injection 10 mg/mL, 5 mL Vial, manufactured by Marsam Pharmaceuticals Inc., to be bioequivalent to Tracrium[®] Injection 10 mg/mL, 5 mL Vial manufactured by Glaxo Wellcome.

The firm should be informed of the above recommendation.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE **/S/** Date: 12/16/96
FT INITIALLED RMHATRE _____

Concur: **/S/** Date: 12/16/96
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

MMakary/12-4-96 wp 74944W.896
cc: ANDA #74-944, original, Makary, HFD-658, Drug File, Division File.

**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 overdose.

e. DOSAGE AND ADMINISTRATION

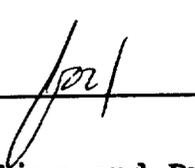
- i. Bolus Doses for Intubation and Maintenance of Neuromuscular Block
 - A). Adults, paragraph 3, sentence 1 - Delete the terminal zero, i.e., ... 0.08 to 0.1 mg/kg ...
 - B). Children and Infants - Delete paragraph 2.
 - C). Special Considerations, paragraph 3, sentence 3 - ... prior to atracurium administration.
- ii. Use by Continuous Infusion, Infusion in the Operating Room (OR) - Combine paragraphs 1 and 2.

Please revise your 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.

NSI



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

RECORD OF TELEPHONE CONVERSATION

<p>I spoke with Ms. Kompa regarding chemistry deficiency and comments from the field chemist.</p> <p>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.</p> <p>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</p>	<p>DATE 7-16-97</p> <hr/> <p>ANDA NUMBERS 74-944 and 74-945</p> <hr/> <p>PRODUCT NAME Atracurium Besylate Injection, Preserved and Non-Preserved</p> <hr/> <p>FIRM NAME Marsam Pharmaceuticals</p> <hr/> <p>NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Jill Kompa</p> <hr/> <p>TELEPHONE NUMBER 609-489-5330</p> <hr/> <p>SIGNATURE <div style="text-align: center;">  Radhika Rajagopalan, Chemistry Reviewer </div> </p>
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X:\NEW\FIRMSAM\MARSAM\TELECONS\74944.013

7/16/97

**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 reinstatement 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 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	
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 NOW SUPPLIED?			X
Was 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?			
Was the firm failed to describe the scoring in the NOW 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	
Was 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 C _{max} , T _{max} , 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		
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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 Grace⁰⁰

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

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
74944

CORRESPONDENCE

ANDAs ✓4-944 (5 mL Single Dose Vial)
74-945 (10 mL multiple dose vial)

Marsam Pharmaceuticals Inc.
Attention: Steven W. Brown, R.Ph.
Building 31, Olney Avenue
P.O. Box 1022
Cherry Hill, New Jersey 08034

SEP 22 1997

|||||

Dear Sir:

This is in reference to your abbreviated new drug applications dated August 21, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Atracurium Besylate Injection, 10 mg/mL.

Reference is also made to your amendments dated May 21, July 18 and 23, 1997.

The applications are deficient and, therefore, not approvable under 21 CFR 314.125(b)(13) because the Center for Drug Evaluation and Research (CDER) is unable to find that the methods used in, and the facilities and controls used for, the manufacturing of the drug product by Marsam Pharmaceuticals in Cherry Hill, NJ complies with current good manufacturing practice (CGMP) regulations. This firm is listed in your application as being responsible for manufacturing the drug product.

Our conclusion is based upon the CGMP findings revealed during an inspection of the facility conducted on March 18 to April 17, 1997, by representatives of our New Jersey District Office and subsequent recommendation from our Division of Manufacturing and Product Quality (DMPQ), Office of Compliance.

Until such time that your Cherry Hill, NJ manufacturing facility can demonstrate to the Agency that the CGMP-related issues associated with the manufacturing of Atracurium Besylate Injection have been corrected and the Agency's concerns are otherwise satisfied, your applications cannot be approved.

You should amend these applications when the CGMP-related issues pertaining to the Cherry Hill manufacturing facility have been satisfactorily resolved. Your amendments submitted in response to this not approvable letter will be considered as a MINOR AMENDMENT provided that the amendments contain no significant additional information necessary to remedy the CGMP deficiencies or to address concerns identified by the investigators. Your

amendments should include a statement from a responsible company official informing us that these applications have been recommended for approval by representatives of the New Jersey district. If, as a result of follow-up inspections related to the ongoing evaluation of this or other applications, it is necessary for you to significantly revise your procedures, controls or practices to correct your deficiencies, then the amendments will be considered to represent a MAJOR AMENDMENT.

The file on these applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the applications. If you have substantial disagreement with our reasons for not approving these applications, you may request an opportunity for a hearing.

Sincerely yours,

IS/

Lr,

9/22/97

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-944

Marsam Pharmaceuticals, Inc.
Attention: Thomas L. Pituk
Building 31, 24 Olney Avenue
P.O. BOX 1022
Cherry Hill NJ 08034
|||||

DEC 23 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Atracurium Besylate Injection, 10 mg/mL, 5 mL Single-dose Vial.

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,



Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-944

Marsam Pharmaceuticals, Inc.
Attention: Thomas L. Pituk
Building 31, 24 Olney Avenue
P.O. Box 1022
Cherry Hill, NJ 08034

SEP 20 1996

|||||

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Atracurium Besylate Injection, 10 mg/mL,
5 mL Single-dose vial

DATE OF APPLICATION: August 21, 1996

DATE OF RECEIPT: August 22, 1996

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 594-1300

Sincerely yours,

/S/

9/20/96

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

ORIG AMENDMENT
U/AM

*noted by
2/11/98*

February 5, 1998

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: **ANDA 74-944**
Atracurium Besylate Injection, 10 mg/mL, 5 mL single dose vial
MINOR AMENDMENT

Dear Sir or Madam:

Reference is made to our abbreviated new drug application dated August 21, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act and in accordance with the provisions of the Regulations 21 CFR§314.94 for Atracurium Besylate Injection, 10 mg/mL, 5 mL single dose vial.

Reference is also made to your not approvable letter dated September 22, 1997, stating that the application was deficient and, therefore, not approvable under 21 CFR§314.125(b)(13). Your letter stated that, based on the CGMP findings revealed during an inspection of our facility and subsequent recommendation from the Division of Manufacturing and Product Quality (DMPQ), Office of Compliance, CDER had determined that Marsam was not in compliance with current good manufacturing practice (CGMP) regulations. Your letter stated that, until such time that we can demonstrate that the problems have been corrected, the application cannot be approved. In addition, you directed us to submit a MINOR AMENDMENT in response to the not approvable letter which includes a statement from a responsible corporate official certifying that our facilities have been found to be in compliance with CGMP and cleared for approval of this drug product by representatives of the local FDA District Office.

In accordance with your request and pursuant to 21 CFR§314.96, we are submitting this MINOR AMENDMENT to provide a statement certifying that our facilities have been reinspected and found to be in compliance with CGMP regulations and cleared for approval of this (and all) drug products by representatives of New Jersey District Office. We are also enclosing a copy of the "Profile System" printout that was supplied to us on February 3, 1997, by Mr. Richard T. Trainor, Compliance Officer, of the NJDO.

RECEIVED
FEB 06 1998

GENERIC DRUGS

Madam 2/10/98

ANDA 74-944

Page 2

Atracurium Besylate Injection, 10 mg/mL, 5 mL single dose vial
MINOR AMENDMENT

We certify that a true copy of this amendment is being sent to our local FDA District Office.

Please advise us if you require any additional information.

Sincerely,
Marsam Pharmaceuticals Inc.



Steven W. Brown, R.Ph.
Director, Regulatory Affairs

SWB

Enclosures

cc: FDA New Jersey District Office (North Brunswick Resident Post)
120 North Center Drive, North Brunswick, NJ 08902

*noted by
4/2/98*

March 30, 1998

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

U/AMC

**Re: Minor Amendment
ANDA 74-944 - Atracurium Besylate Injection
10 mg/mL, 5 mL unpreserved vial**

Dear Sir or Madam:

In response to your not approvable letter dated March 2, 1998, we are submitting this amendment to the Abbreviated New Drug Application for the above referenced product.

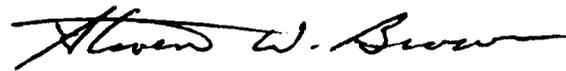
We have responded to each deficiency item by restating each comment (in bold) followed by our response and any necessary attachments.

In accordance with 21 CFR 314.96(b), we hereby certify that a true and complete copy of this amendment is being submitted to our home FDA district office (New Jersey District Office, North Brunswick Resident Post).

We consider this response to adequately address all deficiencies. Should you have any questions or comments regarding this submission, please do not hesitate to contact Jill Kompa at (609) 489-5330.

Sincerely,

Marsam Pharmaceuticals Inc.



Steven W. Brown, R.Ph.
Director, Regulatory Affairs

RECEIVED

MAR 31 1998

GENERIC DRUGS

cc: FDA New Jersey District Office (North Brunswick Resident Post)
120 North Center Drive, North Brunswick, NJ 08902

*Madeline
3-30-98*

*Labeling satisfactory for
approved
Label review drafted
7/31/97 ALG*

UPS

July 23, 1997

FPL

NDA ORIG AMENDMENT

N/AF

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**RE: ANDA 74-944, Atracurium Besylate Injection
10 mg/mL, 5 mL unpreserved vial
FACSIMILE AMENDMENT**

Dear Sir/Madam:

Reference is made to our abbreviated new drug application dated August 21, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act and in accordance with the provisions of the Regulations 21 CFR§314.94 for Atracurium Besylate Injection, 10 mg/mL, 5 mL unpreserved vial.

Reference is also made to your facsimile dated July 9, 1997 requesting additional labeling revisions for the container label, carton and insert for this application.

In accordance with 21 CFR§314.96(a), enclosed are twelve copies of final printed container labels, cartons (trays), and package insert labeling that have been revised to be in accordance with your facsimile request. Additionally, in accordance with 21 CFR§314.94(a)(8)(iv), we have included a side-by-side comparison of our proposed labeling with our last submission with all differences annotated and explained.

In addition, since the package insert also lists the 10 mL, preserved Atracurium Besylate Injection line item (ANDA 74-945), we are also submitting an Amendment to that application for the revised package insert. The 10 mL label and carton (tray) were not requested to be revised and therefore, no final printed labeling are submitted for that application.

RECEIVED

JUL 28 1997

We consider this response to adequately address all deficiencies and to provide final printed labeling. Should you have any questions or comments regarding this submission, please do not hesitate to contact the following:

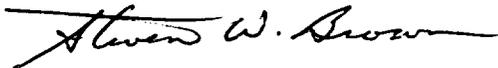
Primary Contact:

Jill Kompa
Senior Regulatory Affairs Associate
Phone: (609) 489-5330
Fax: (609) 424-9418

Secondary Contact:

Anne Toland
Manager, Regulatory Affairs
Phone: (609) 489-5249
Fax: (609) 489-9418

Sincerely,



Steven W. Brown, R.Ph.
Director, Regulatory Affairs

Enclosures

Marsam

PHARMACEUTICALS INC.

UPS OVERNITE

July 18, 1997

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT

RE: ANDA 74-944 and 74-945, Atracurium Besylate Injection
10 mg/mL, 5 mL unpreserved vial
10 mg/mL, 10 mL preserved vial
TELEPHONE AMENDMENT

Dear Sir/Madam:

In response to a telephone call from Radhika Rajagopalan, Reviewing Chemist, OGD with Jill Kompa, Marsam Pharmaceuticals Inc. on July 16, 1997, we are submitting this telephone amendment to both of the Abbreviated New Drug Applications for the above referenced products.

There are two issues we have addressed in this amendment as requested by Ms. Rajagopalan during this telephone conversation. The first issue is in regard to specific questions on the test procedures used to determine the assay and impurities for both the drug substance and drug product. Specifically, these test methods were submitted to the Philadelphia District Laboratory for method validation studies May 12, 1997 along with the preserved finished product samples. Ms. Rajagopalan has notified us that there are several clarifications requested by the laboratory analyst in order to perform the calculations and complete the validation studies. These questions have been addressed in #1- Test Procedures, and copies of the revised test procedures are also included in this submission.

The second issue is to provide additional information concerning the degradation product at RRT of 0.11 present in the finished product. This issue is discussed in #2-Discussion Related to the Unidentified Peak at RRT 0.11. Finally, we have provided a commitment to investigate this issue in order to determine a positive identification of this peak.

RECEIVED

JUL 21 1997

In accordance with 21 CFR 314.96(b), we hereby certify that a true and complete copy of this amendment is being submitted to our home FDA district office (New Jersey District Office, North Brunswick Resident Post).

We acknowledge the labeling deficiency faxed to us July 9, 1997 for Atracurium Besylate Injection, ANDA 74-944. Final printed labeling will be forwarded as soon as it is available.

Should you have any questions or comments regarding this submission, please do not hesitate to contact the following:

Primary Contact:

Jill Kompa
Senior Regulatory Affairs Associate
Phone: (609) 489-5330
Fax: (609) 424-9418

Secondary Contact:

Anne Toland
Manager, Regulatory Affairs
Phone: (609) 489-5249
Fax: (609) 489-9418

Sincerely,



Steven W. Brown, R.Ph.
Director, Regulatory Affairs

Enclosures

cc: FDA New Jersey District Office (North Brunswick Resident Post)
120 North Center Drive, North Brunswick, NJ 08902

May 23, 1997

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

NC

**SUBJECT: MINOR AMENDMENT
ANDA 74-944, Atracurium Besylate Injection
10 mg/mL, 5 mL vial**

Dear Sir/Madam:

This Amendment corresponds to a Minor Amendment for Atracurium Besylate Injection submitted May 21, 1997. That submission erroneously contained a revised Powder & Filled Container Reconciliation Form in the Additional CMC Changes section. Therefore, please replace it with the revised Liquid Filled Container Reconciliation Form enclosed in this submission. We apologize for any confusion this error may have caused.

If you have any questions or comments which can be addressed via telephone and/or telefax, please do not hesitate to contact the following:

Primary Contact

Jill Kompa
Phone: (609) 489-5330
Fax: (609) 424-9418

Alternate Contact

Anne Toland
Phone: (609) 489-5249
Fax: (609) 424-9418

In accordance with 21 CFR Section 314.96(b), Marsam certifies that a true copy of this Amendment is being submitted concurrently to our home FDA District Office (New Jersey District Office, North Brunswick Resident Post).

RECEIVED

MAY 21 1997

MAIL ROOM

Sincerely,



Davis R. Reese
Executive Director,
Scientific & Regulatory Affairs

Madame
5-28-97

Enclosure



NDA ORIG AMENDMENT

*noted MS
5/4/97*

May 21, 1997

*labeling review
drafted 7/1/97
a. v. j. w.*

N/A

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RECEIVED

MAY 22 1997

GENERIC DRUGS

**SUBJECT: ~~MINOR~~ AMENDMENT
ANDA 74-944, Atracurium Besylate Injection
10 mg/mL, 5 mL vial**

Dear Sir/Madam:

In response to your not approvable letter dated May 8, 1997, we are submitting this amendment to the Abbreviated New Drug Application for the above referenced product.

We have responded to each deficiency item by restating each comment (in bold) followed by our response and any necessary attachments. As requested, we have also enclosed final printed labels, trays (cartons) and inserts and a side-by-side comparison of the previous version submitted with the revised version where changes have been made.

Additional CMC changes (other than those made in response to the not approvable letter) and revised documents are located in a separate section entitled "Additional CMC Changes". In particular, we are proposing a change regarding closure sterilization. We have included data for a validated closure sterilization cycle of 121 minutes/17 minutes. Based on this validation, we have revised the production cycle parameters to 122 degrees/20 minutes (i.e., safety in temperature and time).

In accordance with 21 CFR 314.96(b), we hereby certify that a true and complete copy of this amendment is being submitted to our home FDA district office (New Jersey District Office, North Brunswick Resident Post).

We consider this response to adequately address all deficiencies and to provide final printed labeling. Should you have any questions or comments regarding this submission, please do not hesitate to contact the following:

*Madame
5/28/97*

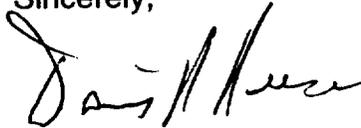
Primary Contact:

Jill Kompa
Associate, Regulatory Affairs
Phone: (609) 489-5330
Fax: (609) 424-9418

Secondary Contact:

Anne Toland
Manager, Regulatory Affairs
Phone: (609) 489-5249
Fax: (609) 489-9418

Sincerely,



Davis R. Reese
Executive Director,
Scientific & Regulatory Affairs

Enclosures

cc: FDA New Jersey District Office (North Brunswick Resident Post)
120 North Center Drive, North Brunswick, NJ 08902

February 24, 1997

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT

NAC

Subject: MAJOR AMENDMENT
ANDA 74-944, Atracurium Besylate Injection
10 mg/mL, 5 mL vial

Dear Sir/Madam:

In response to your not approvable letter dated January 27, 1997, we are submitting this amendment to the Abbreviated New Drug Application for the above referenced product.

We have responded to each deficiency item by restating each comment (in bold) followed by our response and any necessary attachments. Additional CMC changes (other than those made in response to the not approvable letter) and revised documents for the referenced product are listed in the section entitled Additional CMC Changes (see Table of Contents). Many of these changes cover observations made by the district office during the pre-approval inspection for the referenced product which were not covered in your not approvable letter.

In accordance with 21 CFR 314.96(b), we hereby certify that a true and complete copy of this amendment is being submitted to our home FDA district office (New Jersey District Office, North Brunswick Resident Post).

Should you have any questions or comments regarding this submission, please do not hesitate to contact the following:

Primary Contact
Jill Kompa
Associate, Regulatory Affairs
Phone: (609) 489-5330
Fax: (609) 424-9418

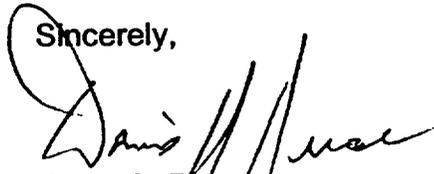
RECEIVED

FEB 27 1997

GENERIC DRUGS

Alternate Contact

Anne M. Toland
Manager, Regulatory Affairs
Phone: (609) 489-5249
Fax: (609) 424-9418

Sincerely,

Davis R. Reese
Executive Director,
Scientific & Regulatory Affairs

Enclosures

cc: FDA New Jersey District Office (North Brunswick Resident Post)
120 North Center Drive, North Brunswick, NJ 08902



505 (S)(2)(a) expiration acceptable for
filing *Carole Marie H. Weikell*
9/6/96

Approved
9/17/96

August 21, 1996

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park, North II
7500 Standish Place, Room 150
Rockville, MD 20855-2733

RECEIVED

AUG 22 1996

GENERIC DRUGS

Re: **NEW ANDA**
Atracurium Besylate Injection, 10 mg/mL
5 mL Single Dose Vial

Dear Sir/Madam:

In accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act, we are submitting the attached Abbreviated New Drug Application (ANDA) for the above referenced product. The listed drug upon which this application is based is Tracrium[®] Injection (Atracurium Besylate) by Glaxo Wellcome Inc. Please note that a separate ANDA is being submitted concurrently for the preserved formulation of this product. Draft labeling is included (Section V) which is based on current approved labeling for Tracrium[®] Injection (Atracurium Besylate). The draft package insert contains both the preserved and unpreserved formulations of Atracurium Besylate Injection, 10 mg/mL; this insert is included in this application and in the ANDA for the preserved product.

This submission consists of two (2) volumes. As required, archival and review copies are provided, and a true copy of the ANDA is being sent concurrently to our home district FDA office. (Please refer to Section XXI for the District Copy Certification and Debarment Certification.) In accordance with Policy and Procedure Guide #30-91, we have included two additional separately bound copies of Section XVI, Analytical Methods, since both the raw material and finished product are not USP Articles. A separate table of contents has been provided for this section and is included in both the ANDA binders and separately bound copies. In addition, to facilitate the microbiological review, pertinent information has been placed in Section XI.2 of the ANDA. A request for waiver of bioequivalence testing is located in Section VI.1.

Included in Section XVII are stability data for the product in the 5 mL vial. Based on the data, we are proposing an 18 month expiration date for this product.

During the course of your review of this application, if you have any questions or comments which can be addressed via telephone and/or telefax, please do not hesitate to contact the following:

Primary Contact

Jill Kompa

Phone: (609) 424-5600, Ext. 330

Fax: (609) 751-8784

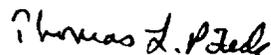
Alternate Contact

Anne Toland

Phone: (609) 424-5600, Ext. 249

Fax: (609) 751-8784

Sincerely,



Thomas L. Pituk
Director, Regulatory Affairs

Enclosures

cc: FDA Newark District Office (North Brunswick Resident Post)
120 North Center Drive, North Brunswick, NJ 08902

Marsam

PHARMACEUTICALS INC.

February 24, 1997

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT

N/A/C

Subject: MAJOR AMENDMENT
ANDA 74-944, Atracurium Besylate Injection
10 mg/mL, 5 mL vial

Dear Sir/Madam:

In response to your not approvable letter dated January 27, 1997, we are submitting this amendment to the Abbreviated New Drug Application for the above referenced product.

We have responded to each deficiency item by restating each comment (in bold) followed by our response and any necessary attachments. Additional CMC changes (other than those made in response to the not approvable letter) and revised documents for the referenced product are listed in the section entitled Additional CMC Changes (see Table of Contents). Many of these changes cover observations made by the district office during the pre-approval inspection for the referenced product which were not covered in your not approvable letter.

In accordance with 21 CFR 314.96(b), we hereby certify that a true and complete copy of this amendment is being submitted to our home FDA district office (New Jersey District Office, North Brunswick Resident Post).

Should you have any questions or comments regarding this submission, please do not hesitate to contact the following:

Primary Contact

Jill Kompa
Associate, Regulatory Affairs
Phone: (609) 489-5330
Fax: (609) 424-9418

RECEIVED

FEB 27 1997

GENERIC DRUGS

imate Contact

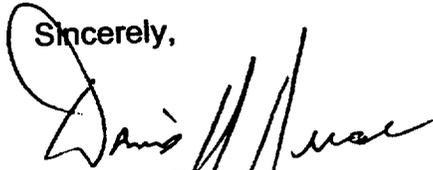
M. Toland

ger, Regulatory Affairs

Phone: (609) 489-5249

(609) 424-9418

Sincerely,



Davis R. Reese
Executive Director,
Scientific & Regulatory Affairs

Enclosures

cc: FDA New Jersey District Office (North Brunswick Resident Post)
120 North Center Drive, North Brunswick, NJ 08902