CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-386/S010

Trade Name:	Brevibloc 100mg/10mL and 2.5g/10ml ampule Injection
Generic Name:	Esmolol Hydrochloride
Sponsor:	Anaquest Inc.
Approval Date:	July 1, 1993
Indications:	Short-Term control of heart rate in patients with abnormally fast heart rhythms such as artrial fibrillation, atrial flutter or sinus tachycardia.

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-386/S-010

Anaquest Inc.
Attention: Ms. Brenda Marczi
110 Allen Road
Liberty Corner, NJ 07938-0804

JUL 1 1993

Dear Ms. Marczi:

We acknowledge the receipt on June 2, 1993 of your June 1, 1993 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Brevibloc (esmolol HCl) 100 mg/10 ml vial and 2.5 g/10 ml ampule Injection.

The supplemental application provides for final printed labeling revised as follows:

1. Under the **PRECAUTIONS/Pregnancy Category C** subsection the first sentence of the second paragraph has been revised to read as follows:

> Although there are no adequate and well controlled studies in pregnant women, use of esmolol in the last trimester of pregnancy or during labor or delivery has been reported to cause fetal bradycardia, which continued after termination of drug infusion. Brevibloc should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

2. The name and address of the sponsor has been changed to:

> Anaquest Inc.
> 110 Allen Road
> PO Box 804
> Liberty Corner, NJ 07938-0804
>
> A subsidiary of BOC Health Care Inc
> BOC Health Care

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Should you have any questions, please contact:

Ms. Zelda McDonald
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

RL 7/1/93

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA
HFD-110
HFD-110/CSO
HFD-80/DDIR
HFD-232 (with labeling)
HFD-110/ZMcDonald/6/15/93;6/16/93 zm 6/30/93
sb/6/15/93;6/30/93
R/D: RWolters/6/21/93
CResnick/6/21/93
SChen/6/21/93
NMorgenstern/6/30/93

Approval Date: December 31, 1986

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-386/S010

LABELING

JUL 1 1993

APPROVED

BREVIBLOC® INJECTION (esmolol hydrochloride)

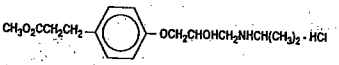
10 mL Ampul–2.5 g
NOT FOR DIRECT INTRAVENOUS INJECTION. AMPUL MUST BE DILUTED PRIOR TO ITS INFUSION - SEE DOSAGE AND ADMINISTRATION.

10 mL Single Dose Vial–100 mg

DESCRIPTION

BREVIBLOC (esmolol HCl) is a beta$_1$-selective (cardioselective) adrenergic receptor blocking agent with a very short duration of action (elimination half-life is approximately 9 minutes). Esmolol HCl is:

(±)-Methyl p-[2-hydroxy-3-(isopropylamino) propoxy] hydrocinnamate hydrochloride and has the following structure:



Esmolol HCl has the empirical formula $C_{16}H_{26}NO_4Cl$ and a molecular weight of 331.8. It has one asymmetric center and exists as an enantiomeric pair.

Esmolol HCl is a white to off-white crystalline powder. It is a relatively hydrophilic compound which is very soluble in water and freely soluble in alcohol. Its partition coefficient (octanol/water) at pH 7.0 is 0.42 compared to 17.0 for propranolol.

BREVIBLOC INJECTION is a clear, colorless to light yellow, sterile, nonpyrogenic solution.

2.5 g, 10 mL Ampul—Each mL contains 250 mg esmolol HCl in 25% Propylene Glycol, USP, 25% Alcohol, USP and Water for Injection, USP; buffered with 17.0 mg Sodium Acetate, USP, and 0.00715 mL Glacial Acetic Acid, USP. Sodium hydroxide and/or hydrochloric acid added, as necessary, to adjust pH to 3.5-5.5.

100 mg, 10 mL Single Dose Vial–Each mL contains 10 mg esmolol HCl and Water for Injection, USP; buffered with 2.8 mg Sodium Acetate, USP and 0.546 mg Glacial Acetic Acid, USP. Sodium hydroxide and/or hydrochloric acid added, as necessary to adjust pH to 4.5-5.5.

CLINICAL PHARMACOLOGY

BREVIBLOC is a beta$_1$-selective (cardioselective) adrenergic receptor blocking agent with rapid onset, a very short duration of action, and no significant intrinsic sympathomimetic or membrane stabilizing activity at therapeutic dosages. Its elimination half-life after intravenous infusion is approximately 9 minutes. BREVIBLOC inhibits the beta$_1$ receptors located chiefly in cardiac muscle, but this preferential effect is not absolute and at higher doses it begins to inhibit beta$_2$ receptors located chiefly in the bronchial and vascular musculature.

Pharmacokinetics and Metabolism

BREVIBLOC is rapidly metabolized by hydrolysis of the ester linkage, chiefly by the esterases in the cytosol of red blood cells and not by plasma cholinesterases or red cell membrane acetylcholinesterase. Total body clearance in man was found to be about 20 L/kg/hr, which is greater than cardiac output; thus the metabolism of BREVIBLOC is not limited by the rate of blood flow to metabolizing tissues such as the liver or affected by hepatic or renal blood flow. BREVIBLOC has a rapid distribution half-life of about 2 minutes and an elimination half-life of about 9 minutes.

Using an appropriate loading dose, steady-state blood levels of BREVIBLOC for dosages from 50-300 mcg/kg/min (.05-0.3 mg/kg/min) are obtained within five minutes. (Steady-state is reached in about 30 minutes without the loading dose.) Steady-state blood levels of BREVIBLOC increase linearly over this dosage range and elimination kinetics are dose-independent over this range. Steady-state blood levels are maintained during infusion but decrease rapidly after termination of the infusion. Because of its short half-life, blood levels of BREVIBLOC can be rapidly altered by increasing or decreasing the infusion rate and rapidly eliminated by discontinuing the infusion.

Consistent with the high rate of blood-based metabolism of BREVIBLOC, less than 2% of the drug is excreted unchanged in the urine. Within 24 hours of the end of infusion, approximately 73-88% of the dosage has been accounted for in the urine as the acid metabolite of BREVIBLOC.

Metabolism of BREVIBLOC results in the formation of the corresponding free acid and methanol. The acid metabolite has been shown in animals to have about 1/1500th the activity of esmolol and in normal volunteers its blood levels do not correspond to the level of beta blockade. The acid metabolite has an elimination half-life of about 3.7 hours and is excreted in the urine with a clearance approximately equivalent to the glomerular filtration rate. Excretion of the acid metabolite is significantly decreased in patients with renal disease, with the elimination half-life increased to about ten-fold that of normals, and plasma levels considerably elevated.

Methanol blood levels, monitored in subjects receiving BREVIBLOC for up to 6 hours at 300 mcg/kg/min (0.3 mg/kg/min) and 24 hours at 150 mcg/kg/min (0.15 mg/kg/min), approximated endogenous levels and were less than 2% of levels usually associated with methanol toxicity.

BREVIBLOC has been shown to be 55% bound to human plasma protein, while the acid metabolite is only 10% bound.

Pharmacodynamics

Clinical pharmacology studies in normal volunteers have confirmed the beta blocking activity of BREVIBLOC, showing reduction in heart rate at rest and during exercise, and attenuation of isoproterenol-induced increases in heart rate. Blood levels of BREVIBLOC have been shown to correlate with extent of beta blockade. After termination of infusion, substantial recovery from beta blockade is observed in 10-20 minutes.

In human electrophysiology studies, BREVIBLOC produced effects typical of a beta blocker; a decrease in the heart rate, increase in sinus cycle length, prolongation of the sinus node recovery time, prolongation of the AH interval during normal sinus rhythm and during atrial pacing, and an increase in antegrade Wenckebach cycle length.

In patients undergoing radionuclide angiography, BREVIBLOC, at dosages of 200 mcg/kg/min (0.2 mg/kg/min), produced reductions in heart rate, systolic blood pressure, rate pressure product, left and right ventricular ejection fraction and cardiac index at rest, which were similar in magnitude to those produced by intravenous propranolol (4 mg). During exercise, BREVIBLOC produced reductions in heart rate, rate pressure product and cardiac index which were also similar to those produced by propranolol, but produced a significantly larger fall in systolic blood pressure. In patients undergoing cardiac catheterization, the maximum therapeutic dose of 300 mcg/kg/min (0.3 mg/kg/min) of BREVIBLOC produced similar effects and, in addition, there were small, clinically insignificant increases in the left ventricular end diastolic pressure and pulmonary capillary wedge pressure. At thirty minutes after the discontinuation of BREVIBLOC infusion, all of the hemodynamic parameters had returned to pretreatment levels.

The relative cardioselectivity of BREVIBLOC was demonstrated in 10 mildly asthmatic patients. Infusions of BREVIBLOC [100, 200 and 300 mcg/kg/min (0.1, 0.2 and 0.3 mg/kg/min)] produced no significant increases in specific airway resistance compared to placebo. At 300 mcg/kg/min (0.3 mg/kg/min), BREVIBLOC produced slightly enhanced bronchomotor sensitivity to dry air stimulus. These effects were not clinically significant, and BREVIBLOC was well tolerated by all patients. Six of the patients also received intravenous propranolol, and at a dosage of 1 mg, two experienced significant, symptomatic bronchospasm requiring bronchodilator treatment. One other propranolol-treated patient also experienced dry air-induced bronchospasm. No adverse pulmonary effects were observed in patients with COPD who received therapeutic dosages of BREVIBLOC for treatment of supraventricular tachycardia (51 patients) or in perioperative settings (32 patients).

Supraventricular Tachycardia
In two multicenter, randomized, double-blind, controlled comparisons of BREVIBLOC with placebo and propranolol, maintenance doses of 50 to 300 mcg/kg/min (0.05 to 0.3 mg/kg/min) of BREVIBLOC were found to be more effective than placebo and about as effective as propranolol, 3-6 mg given by bolus injections, in the treatment of supraventricular tachycardia, principally atrial fibrillation and atrial flutter. The majority of these patients developed their arrhythmias postoperatively. About 60-70% of the patients treated with BREVIBLOC had a desired therapeutic effect (either a 20% reduction in heart rate, a decrease in heart rate to less than 100 bpm, or, rarely, conversion to NSR) and about 95% of those who responded did so at a dosage of 200 mcg/kg/min (0.2 mg/kg/min) or less. The average effective dosage of BREVIBLOC was approximately 100-115 mcg/kg/min (0.1-0.115 mg/kg/min) in the two studies. Other multicenter baseline-controlled studies gave essentially similar results. In the comparison with propranolol, about 50% of patients in both the BREVIBLOC and propranolol groups were on concomitant digoxin. Response rates were slightly higher with both beta blockers in the digoxin-treated patients.

In all studies significant decreases of blood pressure occurred in 20-50% of patients, identified either as adverse reaction reports by investigators, or by observation of systolic pressure less than 90 mmHg or diastolic pressure less than 50 mmHg. The hypotension was symptomatic (mainly diaphoresis or dizziness) in about 12% of patients, and therapy was discontinued in about 11% of patients, about half of whom were symptomatic. In comparison to propranolol, hypotension was about three times as frequent with BREVIBLOC, 53% vs. 17%. The hypotension was rapidly reversible with decreased infusion rate or after discontinuation of therapy with BREVIBLOC. For both BREVIBLOC and propranolol, hypotension was reported less frequently in patients receiving concomitant digoxin.

INDICATIONS AND USAGE

Supraventricular Tachycardia
BREVIBLOC is indicated for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other emergent circumstances where short term control of ventricular rate with a short-acting agent is desirable. BREVIBLOC is also indicated in noncompensatory sinus tachycardia where, in the physician's judgment, the rapid heart rate requires specific intervention. BREVIBLOC is not intended for use in chronic settings where transfer to another agent is anticipated.

Intraoperative and Postoperative Tachycardia and/or Hypertension
BREVIBLOC (esmolol HCl) is indicated for the treatment of tachycardia and hypertension that occur during induction and tracheal intubation, during surgery, on emergence from anesthesia, and in the postoperative period, when in the physician's judgment such specific intervention is considered indicated.

Use of BREVIBLOC to prevent such events is not recommended.

CONTRAINDICATIONS

BREVIBLOC is contraindicated in patients with sinus bradycardia, heart block greater than first degree, cardiogenic shock or overt heart failure (see WARNINGS).

WARNINGS

Hypotension: In clinical trials 20-50% of patients treated with BREVIBLOC have experienced hypotension, generally defined as systolic pressure less than 90 mmHg and/or diastolic pressure less than 50 mmHg. About 12% of the patients have been symptomatic (mainly diaphoresis or dizziness). Hypotension can occur at any dose but is dose-related so that doses beyond 200 mcg/kg/min (0.2 mg/kg/min) are not recommended. Patients should be closely monitored, especially if pretreatment blood pressure is low. Decrease of dose or termination of infusion reverses hypotension, usually within 30 minutes.

Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. Continued depression of the myocardium with beta blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, BREVIBLOC should be withdrawn. Although withdrawal may be sufficient because of the short elimination half-life of BREVIBLOC, specific treatment may also be considered (see OVERDOSAGE). The use of BREVIBLOC for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium. Despite the rapid onset and offset of the effects of BREVIBLOC, several cases of death have been reported in complex clinical states where BREVIBLOC was presumably being used to control ventricular rate.

Intraoperative and Postoperative Tachycardia and/or Hypertension: BREVIBLOC should not be used as the treatment for hypertension in patients in whom the increased blood pressure is primarily due to the vasoconstriction associated with hypothermia.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity and titratability, BREVIBLOC may be used with caution in patients with bronchospastic diseases. However, since beta$_1$ selectivity is not absolute, BREVIBLOC should be carefully titrated to obtain the lowest possible effective dose. In the event of bronchospasm, the infusion should be terminated immediately; a beta$_2$ stimulating agent may be administered if conditions warrant but should be used with particular caution as patients already have rapid ventricular rates.

Diabetes Mellitus and Hypoglycemia: BREVIBLOC should be used with caution in diabetic patients requiring a beta blocking agent. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

PRECAUTIONS

General
Infusion concentrations of 20 mg/mL were associated with more serious venous irritation, including thrombophlebitis, than concentrations of 10 mg/mL. Extravasation of 20 mg/mL may lead to a serious local reaction and possible skin necrosis. Concentrations greater than 10 mg/mL or infusion into small veins or through a butterfly catheter should be avoided.

Because the acid metabolite of BREVIBLOC is primarily excreted unchanged by the kidney, BREVIBLOC should be administered with caution to patients with impaired renal function. The elimination half-life of the acid metabolite was prolonged ten-fold and the plasma level was considerably elevated in patients with end-stage renal disease.

Care should be taken in the intravenous administration of BREVIBLOC as sloughing of the skin and necrosis have been reported in association with infiltration and extravasation of intravenous infusions.

Drug Interactions
Catecholamine-depleting drugs, e.g., reserpine, may have an additive effect when given with beta blocking agents. Patients treated concurrently with BREVIBLOC and a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

A study of interaction between BREVIBLOC and warfarin showed that concomitant administration of BREVIBLOC and warfarin does not alter warfarin plasma levels. BREVIBLOC concentrations were equivocally higher when given with warfarin, but this is not likely to be clinically important.

When digoxin and BREVIBLOC were concomitantly administered intravenously to normal volunteers, there was a 10-20% increase in digoxin blood levels at some time points. Digoxin did not affect BREVIBLOC pharmacokinetics. When intravenous morphine and BREVIBLOC were concomitantly administered in normal subjects, no effect on morphine blood levels was seen, but BREVIBLOC steady-state blood levels were increased by 46% in the presence of morphine. No other pharmacokinetic parameters were changed.

The effect of BREVIBLOC on the duration of succinylcholine-induced neuromuscular blockade was studied in patients undergoing surgery. The onset of neuromuscular blockade by succinylcholine was unaffected by BREVIBLOC, but the duration of neuromuscular blockade was prolonged from 5 minutes to 8 minutes.

Although the interactions observed in these studies do not appear to be of major clinical importance, BREVIBLOC should be titrated with caution in patients being treated concurrently with digoxin, morphine, succinylcholine or warfarin.

While taking beta blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Caution should be exercised when considering the use of BREVIBLOC and verapamil in patients with depressed myocardial function. Fatal cardiac arrests have occurred in patients receiving both drugs. Additionally, BREVIBLOC should not be used to control supraventricular

tachycardia in the presence of agents which are vasoconstrictive and inotropic such as dopamine, epinephrine, and norepinephrine because of the danger of blocking cardiac contractility when systemic vascular resistance is high.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Because of its short term usage no carcinogenicity, mutagenicity or reproductive performance studies have been conducted with BREVIBLOC (esmolol HCl).

Pregnancy Category C
Teratogenicity studies in rats at intravenous dosages of BREVIBLOC up to 3000 mcg/kg/min (3 mg/kg/min) (ten times the maximum human maintenance dosage) for 30 minutes daily produced no evidence of maternal toxicity, embryotoxicity or teratogenicity, while a dosage of 10,000 mcg/kg/min (10 mg/kg/min) produced maternal toxicity and lethality. In rabbits, intravenous dosages up to 1000 mcg/kg/min (1 mg/kg/min) for 30 minutes daily produced no evidence of maternal toxicity, embryotoxicity or teratogenicity, while 2500 mcg/kg/min (2.5 mg/kg/min) produced minimal maternal toxicity and increased fetal resorptions.

Although there are no adequate and well-controlled studies in pregnant women, use of esmolol in the last trimester of pregnancy or during labor or delivery has been reported to cause fetal bradycardia, which continued after termination of drug infusion. BREVIBLOC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether BREVIBLOC is excreted in human milk; however, caution should be exercised when BREVIBLOC is administered to a nursing woman.

Pediatric Use
The safety and effectiveness of BREVIBLOC in children have not been established.

ADVERSE REACTIONS
The following adverse reaction rates are based on use of BREVIBLOC in clinical trials involving 369 patients with supraventricular tachycardia and over 600 intraoperative and postoperative patients enrolled in clinical trials. Most adverse effects observed in controlled clinical trial settings have been mild and transient. The most important adverse effect has been hypotension (see WARNINGS). Deaths have been reported in post-marketing experience occurring during complex clinical states where BREVIBLOC was presumably being used simply to control ventricular rate (see WARNINGS/Cardiac Failure).

Cardiovascular — Symptomatic hypotension (diaphoresis, dizziness) occurred in 12% of patients, and therapy was discontinued in about 11%, about half of whom were symptomatic. Asymptomatic hypotension occurred in about 25% of patients. Hypotension resolved during BREVIBLOC (esmolol HCl) infusion in 63% of these patients and within 30 minutes after discontinuation of infusion in 80% of the remaining patients. Diaphoresis accompanied hypotension in 10% of patients. Peripheral ischemia occurred in approximately 1% of patients. Pallor, flushing, bradycardia (heart rate less than 50 beats per minute), chest pain, syncope, pulmonary edema and heart block have each been reported in less than 1% of patients. In two patients without supraventricular tachycardia but with serious coronary artery disease (post inferior myocardial infarction or unstable angina), severe bradycardia/sinus pause/asystole has developed, reversible in both cases with discontinuation of treatment.

Central Nervous System — Dizziness has occurred in 3% of patients; somnolence in 3%; confusion, headache, and agitation in about 2%; and fatigue in about 1% of patients. Paresthesia, asthenia, depression, abnormal thinking, anxiety, anorexia, and lightheadedness were reported in less than 1% of patients. Seizures were also reported in less than 1% of patients, with one death.

Respiratory — Bronchospasm, wheezing, dyspnea, nasal congestion, rhonchi, and rales have each been reported in less than 1% of patients.

Gastrointestinal — Nausea was reported in 7% of patients. Vomiting has occurred in about 1% of patients. Dyspepsia, constipation, dry mouth, and abdominal discomfort have each occurred in less than 1% of patients. Taste perversion has also been reported.

Skin (Infusion Site) — Infusion site reactions including inflammation and induration were reported in about 8% of patients. Edema, erythema, skin discoloration, burning at the infusion site, thrombophlebitis, and local skin necrosis from extravasation have each occurred in less than 1% of patients.

Miscellaneous — Each of the following has been reported in less than 1% of patients: Urinary retention, speech disorder, abnormal vision, midscapular pain, rigors, and fever.

OVERDOSAGE
Acute Toxicity
A few cases of massive accidental overdosage of BREVIBLOC (esmolol HCl) have occurred due to errors in dilution. These intravenous bolus doses BREVIBLOC of 5000-6250 mcg/kg (5-6.25 mg/kg) over 1-2 minutes have produced hypotension, bradycardia, drowsiness and loss of consciousness. The effects have resolved within 10 minutes, in some cases with administration of a pressor agent.

Because of its approximately 9-minute elimination half-life, the first step in the management of toxicity should be to discontinue the BREVIBLOC infusion. Then, based on the observed clinical effects, the following general measures should also be considered.

Bradycardia: Intravenous administration of atropine or another anticholinergic drug.

Bronchospasm: Intravenous administration of a beta$_2$ stimulating agent and/or a theophylline derivative.

Cardiac Failure: Intravenous administration of a diuretic and/or digitalis glycoside. In shock resulting from inadequate cardiac contractility, intravenous administration of dopamine, dobutamine, isoproterenol, or amrinone may be considered.

Symptomatic Hypotension: Intravenous administration of fluids and/or pressor agents.

DOSAGE AND ADMINISTRATION
2.5 g AMPUL
THE 2.5 g AMPUL IS NOT FOR DIRECT INTRAVENOUS INJECTION. THIS DOSAGE FORM IS A CONCENTRATED, POTENT DRUG WHICH MUST BE DILUTED PRIOR TO ITS INFUSION. BREVIBLOC SHOULD NOT BE ADMIXED WITH SODIUM BICARBONATE. BREVIBLOC SHOULD NOT BE MIXED WITH OTHER DRUGS PRIOR TO DILUTION IN A SUITABLE INTRAVENOUS FLUID. (See Compatibility Section below.)

Dilution: Aseptically prepare a 10 mg/mL infusion by adding two 2.5 g ampuls to a 500 mL container or one 2.5 g ampul to a 250 mL container of a compatible intravenous solution listed below. (Remove overage prior to dilution as appropriate.) This yields a final concentration of 10 mg/mL. The diluted solution is stable for at least 24 hours at room temperature. Note: Concentrations of BREVIBLOC greater than 10 mg/mL are likely to produce irritation on continued infusion (see PRECAUTIONS). BREVIBLOC has, however, been well tolerated when administered via a central vein.

100 mg VIAL
This dosage form is prediluted to provide a ready-to-use 10 mg/mL concentration recommended for BREVIBLOC intravenous administration. It may be used to administer the appropriate BREVIBLOC loading dosage infusions by hand-held syringe while the maintenance infusion is being prepared.

When using the 100 mg vial, a loading dose of 0.5 mg/kg/min for a 70 kg patient would be 3.5 mL.

Supraventricular Tachycardia
In the treatment of supraventricular tachycardia, responses to BREVIBLOC usually (over 95%) occur within the range of 50 to 200 mcg/kg/min (0.05 to 0.2 mg/kg/min). The average effective dosage is approximately 100 mcg/kg/min (0.1 mg/kg/min) although dosages as low as 25 mcg/kg/min (0.025 mg/kg/min) have been adequate in some patients. Dosages as high as 300 mcg/kg/min (0.3 mg/kg/min) have been used, but these provide little added effect and an increased rate of adverse effects, and are not recommended. Dosage of BREVIBLOC in supraventricular tachycardia must be individualized by titration in which each step consists of a loading dosage followed by a maintenance dosage.

To initiate treatment of a patient with supraventricular tachycardia, administer a loading infusion of 500 mcg/kg/min (0.5 mg/kg/min) over one minute followed by a four-minute maintenance infusion of 50 mcg/kg/min (0.05 mg/kg/min). If an adequate therapeutic effect is observed over the five minutes of drug administration, maintain the maintenance infusion dosage with periodic adjustments up or down as needed. If an adequate therapeutic effect is not observed, the same loading dosage is repeated over one minute followed by an increased maintenance infusion rate of 100 mcg/kg/min (0.1 mg/kg/min).

Continue titration procedure as above, repeating the original loading infusion of 500 mcg/kg/min (0.5 mg/kg/min) over 1 minute, but increasing the maintenance infusion rate over the subsequent four minutes by 50 mcg/kg/min (0.05 mg/kg/min) increments. As the desired heart rate or blood pressure is approached, omit subsequent loading doses and titrate the maintenance dosage up or down to endpoint. Also, if desired, increase the interval between steps from 5 to 10 minutes.

Time (minutes)	Loading Dose (over 1 minute) mcg/kg/min	mg/kg/min	Maintenance Dosage (over 4 minutes) mcg/kg/min	mg/kg/min
0-1	500	0.5		
1-5			50	0.05
5-6	500	0.5		
6-10			100	0.1
10-11	500	0.5		
11-15			150	0.15
15-16	*	*		
16-20			*200	*0.2
20-(24 hrs)			Maintenance dose titrated to heart rate or other clinical endpoint.	

* As the desired heart rate or endpoint is approached, the loading infusion may be omitted and the maintenance infusion titrated to 300 mcg/kg/min (0.3 mg/kg/min) or downward as appropriate. Maintenance dosages above 200 mcg/kg/min (0.2 mg/kg/min) have not been shown to have significantly increased benefits. The interval between titration steps may be increased.

This specific dosage regimen has not been studied intraoperatively and, because of the time required for titration, may not be optimal for intraoperative use.

The safety of dosages above 300 mcg/kg/min (0.3 mg/kg/min) has not been studied.

In the event of an adverse reaction, the dosage of BREVIBLOC may be reduced or discontinued. If a local infusion site reaction develops, an alternate infusion site should be used and caution should be taken to prevent extravasation. The use of butterfly needles should be avoided.

Abrupt cessation of BREVIBLOC in patients has not been reported to produce the withdrawal effects which may occur with abrupt withdrawal of beta blockers following chronic use in coronary artery disease (CAD) patients. However, caution should still be used in abruptly discontinuing infusions of BREVIBLOC in CAD patients.

After achieving an adequate control of the heart rate and a stable clinical status in patients with supraventricular tachycardia, transition to alternative antiarrhythmic agents such as propranolol, digoxin, or verapamil, may be accomplished. A recommended guideline for such a transition is given below but the physician should carefully consider the labeling instructions for the alternative agent selected.

Alternative Agent	Dosage
Propranolol hydrochloride	10-20 mg q 4-6 h
Digoxin	0.125-0.5 mg q 6 h (p.o. or i.v.)
Verapamil	80 mg q 6 h

The dosage of BREVIBLOC (esmolol HCl) should be reduced as follows:

1. Thirty minutes following the first dose of the alternative agent, reduce the infusion rate of BREVIBLOC by one-half (50%).

2. Following the second dose of the alternative agent, monitor the patient's response and if satisfactory control is maintained for the first hour, discontinue BREVIBLOC.

The use of infusions of BREVIBLOC up to 24 hours has been well documented; in addition, limited data from 24-48 hrs (N=48) indicate that BREVIBLOC is well tolerated up to 48 hours.

Intraoperative and Postoperative Tachycardia and/or Hypertension
In the intraoperative and postoperative settings it is not always advisable to slowly titrate the dose of BREVIBLOC to a therapeutic effect. Therefore, two dosing options are presented: immediate control dosing and a gradual control when the physician has time to titrate.

1. Immediate Control
   For intraoperative treatment of tachycardia and/or hypertension give an 80 mg (approximately 1 mg/kg) bolus dose over 30 seconds followed by a 150 mcg/kg/min infusion, if necessary. Adjust the infusion rate as required up to 300 mcg/kg/min to maintain desired heart rate and/or blood pressure.

2. Gradual Control
   For postoperative tachycardia and hypertension, the dosing schedule is the same as that used in supraventricular tachycardia. To initiatetreatment administer a loading dosage infusion of 500 mcg/kg/min of BREVIBLOC for one minute followed by a four-minute maintenance infusion of 50 mcg/kg/min. If an adequate therapeutic effect is not observed within five minutes, repeat the same loading dosage and follow with a maintenance infusion increased to 100 mcg/kg/min (see above Supraventricular Tachycardia).

   Note: Higher dosages (250-300 mcg/kg/min) may be required for adequate control of blood pressure than those required for the treatment of atrial fibrillation, flutter and sinus tachycardia. One third of the postoperative hypertensive patients required these higher doses.

Compatibility with Commonly Used Intravenous Fluids
BREVIBLOC INJECTION was tested for compatibility with ten commonly used intravenous fluids at a final concentration of 10 mg esmolol HCl per mL. BREVIBLOC INJECTION was found to be compatible with the following solutions and was stable for at least 24 hours at controlled room temperature or under refrigeration:

Dextrose (5%) Injection, USP
Dextrose (5%) in Lactated Ringer's Injection
Dextrose (5%) in Ringer's Injection
Dextrose (5%) and Sodium Chloride (0.45%) Injection, USP
Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
Lactated Ringer's Injection, USP
Potassium Chloride (40 mEq/liter) in Dextrose (5%) Injection, USP
Sodium Chloride (0.45%) Injection, USP
Sodium Chloride (0.9%) Injection, USP

BREVIBLOC INJECTION was NOT compatible with Sodium Bicarbonate (5%) Injection, USP.

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

HOW SUPPLIED

NDC 10019-015-71, 100 mg — 10 mL vial, Box of 20
NDC 10019-025-18 , 2.5 g — 10 mL ampul, Box of 10

STORE AT CONTROLLED ROOM TEMPERATURE (59° - 86° F, 15° - 30° C). Freezing does not adversely affect the product, but exposure to elevated temperatures should be avoided.

Anaquest Inc
110 Allen Road
PO Box 804
Liberty Corner, NJ 07938-0804

A Subsidiary of BOC Health Care Inc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-386/S010

CHEMISTRY REVIEW(S)

19-386
27.1
S-010
6-1-93

JUN 7 1993

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 19-386
3. Name and Address of Applicant (City & State) Anaquest Inc. 110 Allen Road P.O. Box 804 Liberty Corner, NJ 07938-0804		4. Supplement(s) Number(s) Date(s) S-010 6/1/93 (LR)
5. Drug Name Brevibloc	6. Nonproprietary Name Esmolol hydrochloride	8. Amendments & Other (reports, etc) - Dates
7. Supplement Provides For: Final printed labeling revised to complete the change of ownership procedure under 21 CFR 314.70. Changes under PRECAUTIONS/Pregnancy Category C is revised.		
9. Pharmacological Category Anti-adrenergic (β-receptor)	10. How Dispensed ☐ Rx ☐ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Intravenous injection	13. Potency(ies) 100mg/mL, 250mg/mL 10 mg/mL	
14. Chemical Name and Structure		15. Records/Reports Current ☐ Yes ☐ No Reviewed ☐ Yes ☐ No

16. Comments: SPECIAL SUPPLEMENT: CHANGES BEING EFFECTED
Following revisions are included:

1. The name and address of sponsor was changed to:
Anaquest Inc.
110 Allen Road
P.O. Box 804
Liberty Corner, NJ 07938-0804

A subsidiary of BOC Health Care Inc.
BOC Health Care

1. Second paragraph under PRECAUTIONS/Pregnancy Category C was revised. Revision is include.

No changes under DESCRIPTION and HOW SUPPLIED sections. Insert - 400-277-00 Rev. 5/93 - is included.

17. Conclusions and Recommendations:
Satisfactory for DESCRIPTION and HOW SUPPLIED sections.

18. REVIEWER

Name	Signature	Date Completed
Danute G. Cunningham	Danute G. Cunningham	June 7, 1993

Distribution: ☒ Original Jacket ☐ Reviewer ☐ Division File ☐ CSO

19386S10.SUP

J Wells 6-7-93

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-386/S010

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CSO Review of Final Printed Labeling
NDA 19-386/S-010

Date of Submission: June 1, 1993

JUL 1 1993

Date of Review: June 14, 1993

Applicant Name: Anaquest Inc.

Product Name: Brevibloc (esmolol HCl) Injection

Evaluation:
This submission is a Special Supplement - Changes Being Effected that provides for final printed labeling revised in accordance with our supplement request letter dated April 8, 1993.

Under the PRECAUTIONS/Pregnancy Category C subsection the first sentence of the second paragraph has been revised to read as follows:

> Although there are no adequate and well controlled studies in pregnant women, use of esmolol in the last trimester of pregnancy or during labor or delivery has been reported to cause fetal braycardia, which continued after termination of drug infusion. Brevibloc should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

This wording is not exactly what we requested in our letter of April 8, 1993, however, Drs. Lipicky and Chen agreed to this wording proposed by Anaquest in an April 21, 1993 FAX. See record of telephone conversation dated April 27, 1993.

This submission also completes the change of sponsor procedure from Merck to Anaquest since the new labeling has Anaquest as the sponsor of the drug.

There were no other changes from the last approved package insert.

Recommendation:
An approval letter should issue for this supplement as set forth under 21 CFR 314.70 (c) (2) (i) [To add or strengthen a contraindication, warning, precaution, or adverse reaction].

Zelda McDonald

Zelda McDonald, CSO

cc: Orig. NDAs
HFD-110
HFD-111/McDonald
HFD-111/Benton