CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

19-386

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-386

DEC 31 1986

Dupont Critical Care, Inc.
Attention: Kenneth G. Kasses, Ph.D.
1600 Waukegan Road
Waukegan, IL 60085

Dear Dr. Kasses:

Please refer to your December 31, 1984 new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Brevibloc (esmolol HCl) Injection 250 mg/mL in 10 mL ampules.

We also acknowledge receipt of your amendment dated December 29, 1986.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved effective on the date of this letter.

We acknowledge your commitment made in our December 30, 1986 meeting to conduct post marketing studies to explore the prominent hypotensive effect of esmolol. We suggest comparison of the hemodynamic effects of esmolol to those of propranolol, atenolol and metoprolol. Further details of such a study can be discussed with the Division of Cardio-Renal Drug Products.

Please submit twelve copies of the FPL as soon as available. Please individually mount seven of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FPL Supplement" to the approved NDA 19-386. Approval of this supplement by FDA is not required before the labeling is used.

The final printed labeling (FPL) must be identical to the marked-up draft labeling. Marketing the product with FPL that is not identical to the draft labeling may render the product misbranded and an unapproved new drug.

At the time of the next printing, please increase the type size of esmolol HCl where ever it appears on the outer carton.

Should additional information relating to the safety and effectiveness of the drug become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

In addition, we would appreciate your submitting copies of the introductory promotional material that you propose to use for this product. Please submit one copy to the Division of Cardio-Renal Drug Products and a second, along with a copy of the package insert, directly to:

Division of Drug Advertising and Labeling, HFN-240
Room 10B-04
5600 Fishers Lane
Rockville, Maryland 20857

Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

Please submit one market package of the drug when it is available.

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

If you have any questions, please contact:

Ms. Constance Burner Henry
Consumer Safety Officer
(301) 443-4730

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

Enclosure

BREVIBLOC® INJECTION
(esmolol hydrochloride)

10 mL Ampul — 2.5 g

NOT FOR DIRECT INTRAVENOUS INJECTION. BREVIBLOC® MUST BE DILUTED PRIOR TO USE. REFERENCE SHOULD BE MADE TO FULL PRESCRIBING INFORMATION BEFORE DOSAGE AND ADMINISTRATION.

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:

$$CH_3O_2CCH_2CH_2\text{-}C_6H_4\text{-}OCH_2CHOHCH_2NHCH(CH_3)_2\cdot HCl$$

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® (esmolol HCl) Vial Diluent is a clear, colorless to light yellow, sterile, nonpyrogenic, solution for intravenous infusion after dilution.

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.

CLINICAL PHARMACOLOGY

BREVIBLOC® (esmolol HCl) 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® competes with the beta$_1$ receptors located chiefly in cardiac muscle, but the 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® (esmolol HCl) 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 of drug 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 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 the dosage range and elimination half-life is dose-independent over this range. Steady-state blood levels are maintained during infusion and increase 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 1/15000th 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. Elimination of the acid metabolite is significantly decreased in patients with renal failure. As the elimination half-life increased to about ten fold (full) of normals, and plasma levels considerably elevated.

Methanol blood levels, measured in subjects receiving BREVIBLOC® for up to 6 hours at 300 mcg/kg/min and 24 hours at 150 mcg/kg/min, approximated endogenous levels and were less than 2% of levels routinely observed after ethanol ingestion.

BREVIBLOC® has been shown in vitro 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® (esmolol HCl), 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 Wenckebach cycle length.

In patients undergoing radionuclide angiography, BREVIBLOC® at dosages of 200 mcg/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 steady state dose of 300 mcg/kg/min of BREVIBLOC® produces similar effects, and in addition there were small clinically non-significant 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® (up to 300 mcg/kg/min) produced no significant increases in specific airway resistance compared to placebo. At 300 mcg/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. Two of the patients who received intravenous propranolol, and at a dosage of 1 mg, had 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 (31 patients) or in perioperative settings (32 patients).

Supraventricular Tachycardia

In two multicenter, randomized, double-blind, controlled comparisons of BREVIBLOC® (esmolol HCl) with placebo and propranolol, maintenance doses of 50 to 300 mcg/kg/min of BREVIBLOC® were found to be more effective than placebo and about as effective as propranolol 3-5 mg given by bolus injections in the treatment of supraventricular tachycardia (principally atrial fibrillation and atrial flutter). The majority of these patients developed new 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 or less. The average effective dosage of BREVIBLOC® was approximately 100-115 mcg/kg/min in the two studies. Other multicenter, placebo-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® 5.3% vs. 1.7%. 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® (esmolol HCl) is indicated for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative 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 judgement, the rapid heart rate requires specific intervention. BREVIBLOC® is not intended for use in chronic settings where transfer to another agent is anticipated.

CONTRAINDICATIONS

BREVIBLOC® (esmolol HCl) is contraindicated in patients with severe 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® (esmolol HCl) have had 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 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, the dosage should be reduced or BREVIBLOC® should be withdrawn. Although this dosage adjustment or withdrawal may be sufficient because of the short elimination half-life of BREVIBLOC®, systemic treatment may also be indicated. (See Overdosage.)

Bronchospastic Disease: PATIENTS WITH BRONCHOSPASTIC DISEASE 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 disease. 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; if needed, a beta$_2$ stimulating agent may be administered. If condition warrants, use of a beta$_2$ stimulating agent may be administered prior to and during the infusion of BREVIBLOC®. BREVIBLOC® should be used with particular caution in patients with bronchospastic disease who do not respond to, or who cannot tolerate, other antihypertensive therapy. Since beta$_2$ receptor selectivity is not absolute, BREVIBLOC® should be used with caution in patients receiving a beta$_2$ stimulating 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 venous irritation and thrombophlebitis than concentrations of 10 mg/mL. Concentrations greater than 10 mg/mL should, therefore, be avoided.

Because the acid metabolite of BREVIBLOC® is primarily excreted unchanged by the kidney, BREVIBLOC® (esmolol HCl) 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.

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® (esmolol HCl) 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 digoxin and BREVIBLOC® were concomitantly administered to normal subjects, no effect on resulting blood levels was seen, but BREVIBLOC® steady-state blood levels were increased by 46% in the presence of morphine (as 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 6 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 morphine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Because of its short term usage no carcinogenicity, mutagenicity or reproductive performance studies have been conducted with BREVIBLOC®.

Pregnancy Category C

Teratogenicity studies in rats at intravenous dosages of BREVIBLOC® up to 3000 mcg/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 produced maternal toxicity and lethality in rabbits, intravenous dosages up to 1000 mcg/kg/min for 30 minutes daily produced no evidence of maternal toxicity, embryotoxicity or teratogenicity; while 2500 mcg/kg/min produced maternal maternal toxicity and increased fetal resorptions.

There are no adequate and well controlled studies in pregnant women. 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

Supraventricular Tachycardia

The following adverse reaction rates are based on use of BREVIBLOC® (esmolol HCl) in almost 600 clinical trial patients with supraventricular tachycardia. In addition, over 500 patients have been exposed in clinical studies of other conditions. The most important adverse effect has been hypotension (see Warnings). Most adverse effects have been mild and transient.

Cardiovascular — Symptomatic hypotension (diaphoresis, dizziness) occurred in 12% of patients and therapy was discontinued in about 1.1%; about half of these were symptomatic. Asymptomatic hypotension occurred in about 25% of patients; hypotension resolved during BREVIBLOC® infusion in 63% of these patients and within 30 minutes after discontinuation of infusion in 80% of the remaining patients. Bradycardia accompanied hypotension in 10% of patients. Peripheral ischemia occurred in approximately 1% of patients. Poor 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 myocardial infarction or unstable angina) severe bradycardia/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, amnesia, and lightheadedness were reported in less than 1% of patients. One brief (30 second) episode of grand mal seizure has been reported.

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 been noted in less than 1% of patients. Taste perversion has also been reported.

Skin (Allergic Rash) — Infusion site reactions including inflammation and extravasation were reported in about 8% of patients. Edema, erythema, skin discoloration, and burning at the infusion site 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, chills, pelvic pain, rigors, and fever.

OVERDOSAGE

Acute Toxicity

A single case of accidental overdosage with BREVIBLOC® (esmolol HCl) has occurred. A 5,000 mcg/kg/min dose of BREVIBLOC® instead of the recommended 500 mcg/kg/min loading dose was administered over one minute to a patient with atrial flutter immediately following the infusion, marked decreases in heart rate and blood pressure were observed and the patient became grossly but could be aroused. The infusion rate of BREVIBLOC® was decreased to 5 mcg/kg/min and over the next eight minutes the patient's rhythm converted to normal sinus rhythm and the patient started feeling better. Hypotension persisted for a period of four minutes after decreasing the dosage of BREVIBLOC®. The drug was discontinued 15 minutes following discontinuation of BREVIBLOC®.

Because of its approximately 9-minute elimination half-life, the first step in the event of toxicity should be to discontinue BREVIBLOC® administration. Then, based on the pharmacologic actions, 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 glycosides in those receiving less inadequate cardiac contractility. However, administration of dopamine, dobutamine, isoproterenol or amrinone may be considered.

DOSAGE AND ADMINISTRATION

NOT FOR DIRECT INTRAVENOUS INJECTION. BREVIBLOC® 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.)

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

Dilution: Aseptically remove 20 mL from a 500-mL bottle of one of the intravenous fluids listed below (see Compatibility with Commonly Used Intravenous Fluids) and add the contents of two (2) ampuls of BREVIBLOC® (each containing 2.5 g esmolol hydrochloride). 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 central venous (see Precautions). BREVIBLOC® has, however, been well tolerated when administered via a central vein.

Supraventricular Tachycardia

In the treatment of supraventricular tachycardia, response to BREVIBLOC® usually (over 50%) occurs within the range of 50 to 200 mcg/kg/min. The average effective dosage is approximately 150 mcg/kg/min although dosages as low as 25 mcg/kg/min have been adequate in some patients. Dosages as high as 300 mcg/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 dose, followed by a maintenance dosage.

To initiate treatment of a patient with supraventricular tachycardia, administer a loading dosage infusion of 500 mcg/kg/min of BREVIBLOC® for one minute followed by a 4 min 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.

Continue titration procedure as above repeating loading infusion (500 mcg/kg/min for 1 minute), increasing maintenance infusion by increments of 50 mcg/kg/min (for 4 minutes). As the desired heart rate or a safety end-point (e.g., lowered blood pressure) is approached, omit the loading infusion and reduce incremental dose to maintenance infusion from 50 mcg/kg/min to 25 mcg/kg/min or lower, as is desired, increase interval between titration steps from 5 to 10 minutes.

Maintenance dosages above 200 mcg/kg/min have not been shown to have significantly increased benefit, and the safety at dosages above 300 mcg/kg/min has not been studied.

In the event of an adverse reaction, the dosage of BREVIBLOC® may be reduced or discontinued. If a total infusion rate reduction dosage, an alternative infusion site should be used. The use of indwelling 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 following instructions for the alternative agent selected.

Alternative Agent	Dosage
Propranolol hydrochloride	10-20 mg q 4 h
Digoxin	0.125-0.5 mg q 6 h (p.o. or i.v.)
Verapamil	80 mg q 8 h

The dosage of BREVIBLOC® should be reduced as follows:

1. Thirty minutes following the last dose of the alternative agent, reduce the infusion rate of BREVIBLOC® by one-half (50%).
2. Following the second dose of the alternative agent, measure 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.

Compatibility with Commonly Used Intravenous Fluids

BREVIBLOC® (esmolol HCl) INJECTION was tested for compatibility with eight 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 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
- Sodium Chloride (0.45%) Injection, USP
- Sodium Chloride (0.9%) Injection, USP

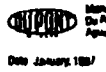
BREVIBLOC® INJECTION was NOT compatible with Sodium Bicarbonate (5%) Injection, USP.

HOW SUPPLIED

BREVIBLOC® (esmolol HCl) INJECTION — 2.5 g (250 mg/mL) is supplied in 10 mL Ampuls

NDC 0004-0826-10 Box of 10

STORE AT CONTROLLED ROOM TEMPERATURE (59°-68°F 15°-30°C). Freezing does not adversely affect the product, but exposure to excessive temperatures should be avoided.



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The Dupont Pharmaceuticals, Inc
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Date January 1987

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M E M O R A N D U M

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics

Date : December 29, 1986

From : Director, Office of Drug Research and Review (HFN-100)

Subject: Esmolol, NDA 19-386

To : Director, Division of Cardio-renal Drug Products (HFN-110)

This is, as you have indicated repeatedly in word and action, a relatively close decision. There is no doubt that esmolol can control ventricular response, at the cost of quite frequent hypotension, and can prevent the rise in heart rate and systolic blood pressure accompanying intubation and some other peri-surgical maneuvers, in this situation with very few side effects.

As you point out, the frequency of hypotension seems greater than expected for a beta-blocker and, indeed, hypotension was much more frequent with esmolol than propranolol in a direct comparison (Study 4).

	n = 64 Esmolol	n = 63 Propranolol
Reported symptomatic	4	1
Reported Asymptomatic	19	3
Total by "criteria"	27	10
Criteria plus reports	34	11

Esmolol is cardioselective, a modest advantage. We have never detected a difference in BP effects between selective and non-selective agents but, in theory, there should be one. The selective agent does not block the peripheral beta-2 dilating effects of circulating catecholamines, while the non-selective agent does, potentially "unmasking" alpha-stimulant (constricting) effects of endogenous catecholamines and maintaining blood pressure. Of course, there is still the question of why we don't see this all the time. Perhaps some reason that catecholamines are especially important to maintaining BP in the SVT setting. It may also be the other drugs present in the perioperative setting render this effect unimportant or it may be that in that setting catecholamines are high and of significance only at those times

(e.g., intubation) when they tend to raise heart rate and BP excessively; the extra vasodilating effect of esmolol is then seen as part of the beneficial effect on HR and BP.

A. Control of SVT

I think the views of the Cardio-Renal Advisory Committee should be given considerable weight, as you have done, in weighing the benefits and risks of esmolol in the SVT setting. The hypotension, while notable and certainly a factor that makes esmolol difficult to use (as does the need to give it by carefully titrated intravenous infusions), is readily reversible and usually asymptomatic. According to the Table I added to p. 67 of the SBA, while evidence of hypotension was present in 20-50% of patients only 6-13% of patients were symptomatic from it. In a direct comparison with propranolol, esmolol did not need to be stopped significantly more often than propranolol. While there were nominally 15 discontinuations due to hypotension in 7 of these there was also a lack of therapeutic response leaving only 8 cases of clear-cut discontinuation due to an adverse effect. There were 6 discontinuations from the propranolol group, for worsened CHF (2), sinus bradycardia (1), and nausea (3), alone (1) or accompanied by hypotension (1), or vomiting and headache (1). All-in all, then, the hypotension, while a management problem, did not result in a significantly greater rate of discontinuations.

The hypotension is also, under the closely monitored circumstances in which the drug is given, not unduly dangerous. There is no SVT patient described in the MOR (covering the original submission and the first safety update) or reported in subsequent safety updates [I have reviewed all early drop-outs in the 1986 safety updates (second and third)] who got into serious difficulty from the hypotension. That now represents 381 esmolol patients in the 04, 05, 07, 12/20/36, and 31 studies and, in the third safety update (which includes cases in the second safety update), another 72 + patients with SVT and other relevant diseases. There were two deaths in these studies each occurring well after esmolol (1 case) or propranolol (1 case) was discontinued. The esmolol patient had possible alcoholic cardiomyopathy and atrial fibrillation. She developed hypotension (causing esmolol to be stopped) although she had converted to NSR and had a persistent tachycardia of about 115 and a BP of about 100/60 after esmolol was stopped. Nine hours after discontinuation she developed intractable VT/VF. The investigator expressed great certainty that the drug played no role in the death or ventricular arrhythmia.

Many other patients with heart disease (not counting those in the surgery studies) also received esmolol, including 44 in hemodynamic and electrophysiology studies 13, 14, and 15, and about one hundred in various studies in unstable angina, CAD, or AMI.

The two patients who got into difficulty, one considerable difficulty, were not SVT patients but patients with significant CAD. One was a patient in Keefe's AMI study (Study 67, patient 1) with recent inferior MI, who developed sinus bradycardia, hypotension and sinus pauses of up to 7.5 sec. Before recovery (7 minutes after infusing esmolol) BP fell to 70 systolic (from 116/80) and HR to 35-40. It would be hard to tell what problem was primary but patients with inferior infarctions are susceptible to bradycardia, sinus arrest, etc., probably with any beta blocker. The 7 minute recovery time is probably shorter than would have been seen with other agents.

The second patient who developed severe problems was a patient in Hallis' unstable angina study (Study 69, patient 1) whose heart rate fell to 70, BP to 84/50 (had been 120/50-53) during infusion. The infusion was slowed, then stopped, but BP fell to 62/30, and HR gradually fell to 40, then 30, then 11, then 0. Atropine reversed all this, along with 15 seconds of CPR. It is again difficult to know what the primary event was. It would seem BP was allowed to stay down too long but it was the HR effect, which is not a unique effect of esmolol, that was probably more important than the BP effect.

The hypotension thus seems to have been manageable and the short recovery time appears to be an advantage that can compensate for the excess hypotension. The alternative therapies, such as propranolol or verapamil can also cause excessive hypotension, even if less frequently, as the propranolol study and study 59 (esmolol vs verapamil) show. With regard to the latter study, not yet reported to us in full, the third safety update reports 4 hypotension (2 moderate, 2 mild) on esmolol vs 6 (3 moderate, 3 mild) on verapamil, among about 20 patients treated during the reporting period.

As you point out, any advantage/benefit of esmolol applies most clearly where treatment is expected to be short term, not where chronic therapy is planned. It would be tempting, of course, to consider esmolol a possible beta-blocker "test dose", but at this point it would seem potentially misleading, perhaps implying (by causing hypotension), intolerance to those agents where general intolerance is not truly present.

In sum, with proper labeling and patient selection, I agree with you and the Committee that esmolol should be approved for rapid control of ventricular rate in short-term circumstances.

Robert Temple

Robert Temple, M.D.

cc:
NDA 19-386
HFN-110/CSO
HFN-101/Dr. Botstein

ODRP:RTemple:eks
12/23/86 0564d
F/T:eks ~~12/30/86~~

HFN-110

29 1986

NDA 19-386

Du Pont Critical Care Inc.
Attention: Kenneth G. Kasses, Ph.D.
1600 Waukegan Road
McGaw Park, IL 60085

Dear Dr. Kasses:

Please refer to your December 31, 1984 new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Brevibloc (esmolol HCl) Injection.

We also acknowledge receipt of your October 31 and November 30, 1984 presubmissions of chemistry information and your amendments dated February 4, 8 and 28, March 13, May 2 and 14, July 22, August 2, 20, 26 and 29, October 7, November 8, 12, 20 and 26, 1985; January 17, March 5 and 24, April 22, May 9, September 11, 15 and 19, October 23, November 7, and December 8, 1986.

We have completed our review of this application as submitted with draft labeling and find the data submitted are sufficient to warrant approval of esmolol for short term control of ventricular rate in patients with atrial flutter/fibrillation.

Although the use of esmolol for this indication is approvable, the prominent hypotensive effect of esmolol requires explanation through postmarketing study. We suggest comparison of the hemodynamic effects of esmolol to those of propranolol, atenolol and metoprolol. Details of such a study can be discussed with the Division of Cardio-Renal Drug Products.

Before the application can be approved, however, it will be necessary for you to submit final printed labeling. The labeling should be essentially identical in content to the enclosed marked-up draft. In addition, please use the second chemical name listed in USAN (±)-Methyl p-[2-hydroxy-3-(isopropylamino) propxy] hydrocinnamate hydrochloride to show that it is a racemate.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

In addition, we would appreciate your submitting copies of the introductory promotional material that you propose to use for this product. Please submit one copy to the Division of Cardio-Renal Drug Products and a second, along with a copy of the package insert, directly to:

Division of Drug Advertising and Labeling, HFN-240
Room 10B-04
5600 Fishers Lane
Rockville, Maryland 20857

Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

Please submit twelve copies of the printed labels and other labeling seven of which are individually mounted on heavy weight paper or similar material.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Ms. Constance Burner Henry
Consumer Safety Officer
Telephone: (301) 443-4730

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

Enclosure

cc:
Original NDA
HFN-110
HFN-110/CSO
HFN-240 (with draft labeling)
HFN-83
HFN-100/Dr. Temple
HFN-110/CHenry/4/3/86;5/16/86;7/28/86;7/29/86;11/20/86
sb/4/7/86;5/16/86;5/20/86;7/28/86;7/28/86;7/29/86;11/20/86/3242s
R/D: GBuehler/5/9/86
GJohnson/5/14/86;7/28/86;7/29/86
CResnick/5/14/86
RVishnuvajjala/5/16/86
RLiberman/5/13/86;7/28/86
RWolters/5/14/86;7/28/86;7/29/86
MMorgenstern/5/16/86;7/29/86;7/29/86;11/21/86
Revised by RLipicky/7/28/86;7/28/86;7/28/86;11/19/86
VGlocklin/7/31/86
CKumkumian/8/5/86

APPROVABLE

BREVIBLOC®

(esmolol hydrochloride)

INJECTION

10 mL Ampul - 2.5 g

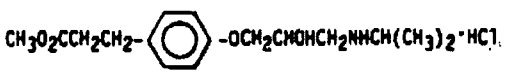
NOT FOR DIRECT INTRAVENOUS INJECTION. BREVIBLOC® MUST BE DILUTED PRIOR TO ITS INFUSION (SEE DOSAGE AND ADMINISTRATION SECTION).

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] ~~phenyl] propionate~~ hydrocinnamate hydrochloride

and has the following structure:



$CH_3O_2CCH_2CH_2-C_6H_4-OCH_2CHOHCH_2NHCH(CH_3)_2 \cdot HCl$

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® (esmolol HCl) INJECTION is a clear, colorless to light yellow, sterile, nonpyrogenic solution for intravenous infusion after dilution. It has a pH range of 3.5 to 5.5.

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.

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 ~~however~~ and at higher doses it begins to inhibit $beta_2$ receptors located chiefly in the bronchial and vascular musculature. ~~Thus Brevibloc® preferentially inhibits the chronotropic and inotropic responses to beta-adrenergic stimulation.~~

Pharmacokinetics and Metabolism

Using an appropriate loading dose, steady-state blood levels of Brevibloc® for dosages from 50-300 mcg/kg/min are obtained within five minutes. Blood levels of Brevibloc® increase linearly over this dosage range. Steady-state blood levels are maintained during infusion but decrease rapidly after termination of the infusion. ~~The elimination half-life of Brevibloc® after intravenous infusion is approximately 9 minutes.~~ Thus, 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.

Brevibloc® is metabolized 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, ~~since this is~~ greater than cardiac output, the metabolism of Brevibloc® is not limited by the rate of blood flow to metabolizing tissues such as the liver. Brevibloc® has a rapid distribution half-life of about 2 minutes. 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®. ~~Elimination kinetics of Brevibloc® have been found to be independent of the dosage in the range of 50 to 300 mcg/kg/min.~~

Metabolism of Brevibloc® ~~occurs via hydrolysis of the ester moiety~~ results in the formation of the corresponding free acid and methanol. The ~~kinetics of~~ The acid metabolite ~~have been found to be independent of the dose while its~~ has an elimination half-life of about 3.7 hours and ~~is excreted in the urine with a clearance~~ ~~total body clearance of the metabolite is~~ approximately equivalent to the glomerular filtration rate. Methanol blood levels, monitored in subjects receiving Brevibloc® for up to 6 hours at 300 mcg/kg/min and 24 hours at 150 mcg/kg/min, approximated endogenous levels and were less than 2% of levels usually associated with methanol toxicity. ~~The pharmacokinetics of Brevibloc® have also been evaluated in patients with hepatic disease (cirrhosis) and end-stage renal disease and were unchanged in these patients compared to those in normal subjects.~~

~~The pharmacokinetics~~ Excretion of the acid metabolite is ~~however, were~~ significantly ~~different~~ decreased in patients with renal disease, with the elimination half-life ~~in these patients was~~ increased about ten times that of normals, and the plasma levels were considerably elevated.

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

metabolite has been shown in animals to have about 1/1500 th the activity of esmolol and in normal volunteers its blood levels do not correspond to the level of beta blockade.

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. Brevibloc blood levels 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, produced reductions in heart rate, systolic blood pressure rate pressure product, at rest left and right ventricular ejection fraction and cardiac index 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 of Brevibloc® produced ~~decreases in the heart rate, systolic blood pressure, rate-pressure product, left ventricular ejection fraction, and cardiac index~~ 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 and in patients with chronic obstructive pulmonary disease (COPD). In mildly asthmatic~~ patients, Brevibloc® infusions (100, 200 and 300 mcg/kg/min) produced no significant increases in specific airway resistance ~~when~~ compared to placebo. At 300 mcg/kg/min, Brevibloc® produced slightly enhanced bronchomotor sensitivity to dry air stimulus. These effects were not clinically significant, and Brevibloc® was well tolerated by ~~these~~ all patients. ~~No patients were discontinued from the study~~. Six of these 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).

~~In a study in patients with elevated heart rates and acute ischemic~~ heart disease (unstable angina pectoris or ~~acute~~ myocardial infarction), Brevibloc®, when titrated ~~from~~ 50 to 300 mcg/kg/min lowered heart rate and blood pressure; and had no significant effect on left ventricular filling pressure or systemic vascular resistance, but decreased cardiac index. Cardiac index returned to pretreatment ~~levels within 30 minutes after discontinuation of the infusion.~~ ~~Following loading and maintenance infusions of Brevibloc®, blood~~ levels and beta blockade are at steady state within 5 minutes. If a loading dosage is not used, approximately 30 minutes is required to ~~reach steady-state blood levels. Brevibloc® blood levels have also~~ moved

~~been correlated with levels of beta blockade. After termination of Brevibloc® infusions, substantial recovery from beta blockade has been observed within 10 to 30 minutes.~~

~~The acid metabolite of Brevibloc® has been shown in animals to have~~ 1/1580th the beta-blocking potency of Brevibloc®. In normal volunteers no correlations have been observed between the blood levels of this metabolite and beta blockade following the administration of ~~Brevibloc®~~.

Supraventricular Tachycardia

In ~~a~~ randomized, double-blind, ~~placebo~~-controlled ~~multicenter study~~ comparisons of Brevibloc®, ~~in~~ maintenance dosages of 50 to 300 mcg/kg/min ~~was~~ found to be more effective than placebo in the treatment of supraventricular tachycardia, ~~such as~~ atrial flutter, ~~atrial fibrillation, and sinus tachycardia. Sixty-four (64) percent~~ of the Brevibloc-treated patients had a desirable therapeutic effect (either a 20% reduction in heart rate, a decrease in heart rate to less than 100 bpm, or conversion to NSR) and ~~95%~~ of ~~these respondents~~ did so at a dosage of 200 mcg/kg/min or less. The average effective dosage of Brevibloc® was approximately 100 mcg/kg/min.

~~In another randomized, double-blind, multicenter trial, in which~~ patients with supraventricular tachycardia received either Brevibloc® or propranolol, Brevibloc® in dosages of 50 to 300 mcg/kg/min was found to be comparable in efficacy to propranolol, 3 to 6 mg given by ~~intravenous bolus injection. Seventy-two (72) percent of the~~

~~Brevibloc® and 60% of the propranolol-treated patients achieved a~~ therapeutic response, and 97% of the patients who responded to Brevibloc® had a therapeutic response at doses of 200 mcg/kg/min or less. The average effective dosage of Brevibloc® in this study was approximately 115 mcg/kg/min.

In a large, base line-controlled study, Brevibloc® was infused at dosages of 25 to 300 mcg/kg/min for periods up to 24 hours. The effective dosage that produced either a 15% reduction in the heart rate or a conversion to NSR ranged from 25 to 200 mcg/kg/min with 79% of patients responding, and 95% of the responders did so at 200 mcg/kg/min or less. In another multicenter trial, patients controlled on Brevibloc® were transferred to one of several oral or intravenous antiarrhythmic agents for chronic treatment of supraventricular ~~tachycardias (See Dosage and Administration).~~

In all studies, significant decreases of blood press occurred in 20-50% of patients, identified either as adverse reaction reports by investigators or by observation of systolic pressure less than 90 mm Hg or diastolic pressure less than 50 mm Hg. The hypotension was symptomatic in about 0.2% of patients and led to discontinuation of therapy in about 1%. In comparison to propranolol, hypotension was about three times as frequent with esmolol, 5.3% vs 1.7%. The hypotension was rapidly reversible with decreased infusion rate or discontinuation of esmolol therapy. For both esmolol and propranolol hypotension was reported less frequently in patients receiving concomitant digoxin

~~Perioperative Tachycardia and Hypertension~~

~~In three multicenter, randomized, double-blind, placebo-controlled studies, Brevibloc® (500 mcg/kg/min for 4 minutes followed by 300 mcg/kg/min) was found to be effective in inhibiting the increases in heart rate, systolic and mean arterial blood pressures, and rate-pressure product following endotracheal intubation. Brevibloc® reduced the incidence of clinically significant increases in heart rate (≥ 100 bpm) and systolic blood presure (> 160 mmHg) following intubation when compared to placebo. Brevibloc® was well tolerated without significant adverse effects.~~

~~In a fourth multicenter, randomized, double-blind, placebo-controlled~~ trial in patients undergoing coronary artery bypass grafting, Brevibloc® (500 mcg/kg/min for 2 minutes followed by 200 mcg/kg/min was found to be effective in reducing the tachycardia and hypertension and the increase in rate pressure product associated with various stimuli occurring between the period prior to induction of anesthesia and the start of cardiopulmonary bypass surgery. In addition, the patients receiving Brevibloc also required significantly less supplemental inhalation anesthetic and less pharmacological intervention to maintain heart rate or arterial blood pressure. When compared to placebo, Brevibloc® reduced the incidence of clinically significant increases in heart rate (≥100 bpm) and systolic blood pressure (≥160 mmHg). ~~Brevibloc was well tolerated in this study.~~

INDICATIONS AND USAGE

Supraventricular Tachycardia

Brevibloc® is indicated for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter, ~~and sinus tachycardia~~ post-operative ~~catecholamine induced sinus tachycardia~~ in perioperative, or other circumstances short-term emergent ~~situations~~ where ~~rapid~~ control of ventricular rate is desirable with a short-acting agent is ~~desirable~~. Brevibloc is not intended for use in chronic settings ~~where titration to appropriate chronic stable, long-acting agent~~ where transfer to another agent is anticipated. ~~that may be withdrawn rapidly. Examples would include patients with minimal degrees of ventricular dysfunction, or with possible disorders of the cardiac pacemaker or conduction system. (See Precautions.)~~

CONTRAINDICATIONS

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

WARNINGS

Hypotension:

Cardiac 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, the dosage should be reduced or Brevibloc® should be withdrawn. Although this dosage adjustment or withdrawal may be sufficient because of the short elimination half-life of Brevibloc®, specific treatment may also be considered. (See Overdosage.)

In clinical trials, 20-50% of patients treated with Brevibloc have had hypotension, generally defined as a systolic pressure of less than 90 mmHg and/or a diastolic pressure of less than 50 mmHg. This does not appear to be related solely to beta-blockade, as propranolol, at similar beta-blocking doses, caused hypotension about one-third as often. About 1-2% of hypotensive patients have been symptomatic. Hypotension can occur at any dose but is dose-related so that doses beyond 200 mcg/kg/min are not recommended. Patients should be closely monitored, especially if pretreatment blood pressure is low. Decrease of dose or termination of Brevibloc infusion reverses hypotension, usually within 30 minutes.

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.

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 and 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.

Brevibloc® has been given to a limited number of patients with mild manifestations of the above three conditions without exacerbation of the respective existing condition. This experience includes 45 patients with mild CHF, 42 patients with mild COPD and 37 patients with diabetes mellitus.

PRECAUTIONS

General

~~In patients with supraventricular tachycardias, Brevibloc® has been shown to produce a decrease in systolic blood pressure. Accordingly, patients with low pretreatment systolic pressures should be carefully observed during titration and maintenance infusions with Brevibloc®.~~ Included in warnings

Infusion concentrations of 20 mg/mL ~~have been associated with significantly more~~ were ~~than~~ venous irritation and thrombophlebitis ~~in animals, therefore,~~ concentrations greater than 10 mg/mL should be avoided. plasma concentrations of 10 mg/ml

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.

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.

An interaction study 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 concomittantly 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 the Brevibloc® steady-state blood levels were increased by 46% in the presence of morphine, but 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.

The hypotensive effects of inhalation anesthetic agents may be increased in the presence of Brevibloc®. The dosage of either agent may be modified as needed to maintain the desired hemodynamics.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Because of its short term usage no carcinogenicity, mutagenicity or reproductive performance studies have been conducted with Brevibloc®.

Pregnancy Category C

Teratogenicity studies in rats at intravenous dosages of Brevibloc® hydrochloride up to 3000 mcg/kg/min (ten times the maximum recommended 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 produced maternal toxicity and lethality. In rabbits, intravenous dosages up to 1000 mcg/kg/min for 30 minutes daily produced no evidence of maternal toxicity, embryotoxicity or teratogenicity, while 2500 mcg/kg/min produced minimal maternal toxicity and increased fetal resorptions.

There are no adequate and well controlled studies in pregnant women. 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

Supraventricular Tachycardia

The following adverse reaction rates are based on use of Brevibloc® in about 400 clinical trial patients with supraventricular tachycardia. In addition, a total of _____ patients have been exposed in clinical studies of other conditions. Most adverse effects have been mild and transient.

The most common and important adverse effect was hypotension (See warnings)

Cardiovascular - symptomatic hypotension (diaphoresis, dizziness) occurred in 12% of patients and required discontinuation of therapy in about 1% . Asymptomatic hypotension occurred in about 25% of patients. Hypotension resolved during the Brevibloc® 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 severe 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. One brief (30 second) episode of grand mal seizure has been reported.

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, and burning at the infusion site 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.

Perioperative Tachycardia and Hypertension

Of the patients treated with Brevibloc® in operative settings (N=898), very few adverse effects have been reported. The most commonly observed adverse effect was mild hypotension in 4% of patients. The other reported adverse effect was bradycardia (heart rate less than 50 bpm), which occurred in less than 1% of patients. None of these adverse effects was severe, and all resolved soon after discontinuation of Brevibloc®.

OVERDOSAGE

Acute Toxicity

A single case of accidental overdosage with Brevibloc® has occurred to date. A 5000 mcg/kg/min dose of Brevibloc® instead of the recommended 500 mcg/kg/min loading dose, was administered over one minute to a patient with atrial flutter. Immediately following the infusion, marked decreases in heart rate and blood pressure were observed and the patient became drowsy but could be aroused. The infusion rate of Brevibloc® was decreased to 5 mcg/kg/min and over the next eight minutes the patient's rhythm converted to normal sinus rhythm and the patient started feeling better. Hypotension persisted for a period of four minutes after decreasing the dosage of Brevibloc®. The drowsiness disappeared 15 minutes following discontinuation of Brevibloc®.

Because of its approximately 9-minute elimination half-life, the first step in the event of toxicity should be to discontinue Brevibloc® administration. Then, based on the pharmacologic actions, 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.

DOSAGE AND ADMINISTRATION

NOT FOR DIRECT INTRAVENOUS INJECTION. BREVIBLOC® 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.)

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

Dilution: Aseptically remove 20 mL from a 500-mL bottle of one of the intravenous fluids listed below (see Compatibility with Commonly Used Intravenous Fluids), and add the contents of two (2) Brevibloc® ampuls (each containing 2.5 g esmolol hydrochloride). This yields a final concentration of 10 mg/mL. The diluted solution is stable for at least 24 hours at room temperature. Note: Brevibloc® concentrations of 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.

Supraventricular Tachycardia

For the treatment of supraventricular tachycardia, Brevibloc® is usually effective within the range of 50 to 200 mcg/kg/min. The average effective dosage is approximately 100 mcg/kg/min, although dosages as high as 300 mcg/kg/min have been used. ~~In some patients, a dosage of 25 mcg/kg/min has been adequate. For this reason, Brevibloc®~~ dosage 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 dosage infusion of 500 mcg/kg/min of Brevibloc® for one minute followed by a 4 min. 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.

Continue titration procedure as above, repeating loading infusion (500 mcg/kg/min for 1 minute), increasing maintenance infusion by increments of 50 mcg/kg/min (for 4 minutes). As the desired heart rate or a safety end-point (e.g., lowered blood pressure) is approached, omit loading infusion and reduce incremental dose in maintenance infusion from 50 mcg/kg/min to 25 mcg/kg/min or lower. Also, if desired, increase interval between titration steps from 5 to 10 minutes.

Maintenance dosages above 200 mcg/kg/min have not been shown to have significantly increased benefits, and the safety of dosages above 300 mcg/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 alternative infusion site should be used. 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 discontinuing Brevibloc® infusions abruptly 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® should be reduced as follows:

1. Thirty minutes following the first dose of the alternative agent, reduce the Brevibloc® infusion rate 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 the Brevibloc® infusion.

The use of Brevibloc® infusions 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.

~~Perioperative Tachycardia and Hypertension~~

~~In those perioperative settings where it is not possible to titrate~~ Brevibloc® to the desired therapeutic effect, such as induction, ~~intratracheal intubation and surgical manipulations, to obtain a rapid~~

Ideally, Brevibloc® should be infused in a loading dosage of 500 mcg/kg/min for four minutes followed by a maintenance dosage of 300 mcg/kg/min. If a lower dose is desired, for example, in the presence of high-dose narcotic anesthesia, the loading dosage of 500 mcg/kg/min may be reduced to 2 minutes and the maintenance dosage to 200 mcg/kg/min. If necessary, the dosage may be subsequently reduced.

The hypotensive effects of inhalation anesthetic agents may be increased in the presence of Brevibloc®. The dosage of either agent may be modified as needed to maintain the desired hemodynamics.

Compatibility with Commonly Used Intravenous Fluids

BREVIBLOC® (esmolol HCl) INJECTION was tested for compatibility with eight 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 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
Sodium Chloride (0.45%) Injection, USP
Sodium Chloride (0.9%) Injection, USP

BREVIBLOC® INJECTION was NOT compatible with Sodium Bicarbonate (5%)