CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-386/S001 and S002

Trade Name: Brevibloc Injection

Generic Name: Esmolol Hydrochloride

Sponsor: Dupont Critical Care, Inc.

Approval Date: August 15, 1988

Indications: Short-Term control of heart rate in patients with abnormally fast heart rhythms such as artrial fibrillation, atrial flutter or sinus tachycardia.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
19-386/S001 and S002

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-386/S001 and S002

APPROVAL LETTER

S-002 AP 8/3
S-001 AP 8/3 10/17/8 10/29/8

AUG 15 1988

NDA 19-386/S-004
S-006

DuPont Critical Care, Inc.
Attention: Mr. John H. Waterman
1600 Waukegan Rd.
Waukegan, IL 60085

Dear Mr. Waterman:

Please refer to your September 17, 1987 and July 12, 1988 supplemental new drug applications 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 amendments to your September 17 supplemental application dated November 19, 1987, March 10 and June 17, 30, 1988. The latter contained final printed labeling.

Your September 17 supplemental application provides for a new dosage form of Brevibloc (esmolol HCl) consisting of a 10 mL single use vial containing esmolol HCl 10 mg/mL (total of 100 mg) suitable for direct intravenous injection.

Your July 12 supplemental application provides for final printed labeling revised to strengthen the Overdosage and Dosage and Administration sections of the package insert for Brevibloc.

We have completed the review of these supplemental applications and they are 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.

Sincerely yours,

R Z 8/10/88

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-100
HFD-232 (with labeling)
HFD-730
HFD-110/KBongiovanni/7/11/88;8/1/88
clb/7/11/88;8/3/88/0850C
R/D: DCunningham/8/1/88
RWolters/8/1/88
CResnick/8/1/88
SChen/8/1/88
CGraham/8/1/88
NMorgenstern/8/2/88

K. Bongiovanni 8-3-88

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-386/S001 and S002

APPROVABLE LETTER

17.1

NDA 19-386/S-001
/S-002

AUG 4 1987

DuPont Critical Care, Inc.
Attention: Mr. John H. Waterman
1600 Waukegan Road
Waukegan, IL 60085

Dear Mr. Waterman:

Please refer to your January 21, 1987 supplemental new drug applications submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Brevibloc (esmolol hydrochloride) Injection. We also acknowledge receipt on March 3, 1987 of your supplemental new drug application (S-002) dated February 13, 1987.

This letter also confirms your July 27, 1987 telephone conversation with Mr. Gary Buehler. He advised you that for administrative purposes, we have renumbered your January 21 supplemental application.

The supplemental applications provide for :

January 21, 1987/S-001 — An additional dosage form of a 10 mL single dose vial of Brevibloc (esmolol hydrochloride) Injection.

February 13, 1987/S-002 — Final printed labeling revised as follows:

1. "Dextrose (5%) in Lactated Ringer's Injection" will be added to the list of intravenous fluids into which Brevibloc may be diluted.

2. "This specific dosage and administration regimen has not been studied intraoperatively and, because of the time required for titration, may not be optimal for intraoperative use." will be inserted as a fourth paragraph under DOSAGE AND ADMINISTRATION - Superventricular Tachycardia.

We have completed the review of these supplemental applications as submitted with draft labeling. Before these supplements may be approved, however, it will be necessary for you to submit vial and outer carton labels and final printed labeling. 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.

Please submit twelve copies of the printed labels and 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 these supplemental applications, 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 these supplemental applications.

Brevibloc (esmolol hydrochloride) injection in 10 ml single use vials may not be legally marketed until you have been notified in writing that this supplemental application is approved.

Should you have any questions, please contact:

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

Sincerely yours,

R f 7/31/87

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

cc:
Original NDA
HFN-110
HFN-110/CSO
HFN-713/GChi
HFN-80/DDIR
HFN-110/SHalvorsen/7/2/87
clb/7/2/87;7/31/87/1555k
R/D Init.: GBuehler/7/6/87;7/27/87
SHalvorsen/7/6/87;7/21/87;7/23/87 S. Halvorsen 7/31/87
RWolters/7/7/87;7/27/87
NMorgenstern/7/28/87 nam 7/31/87

APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-386/S001 and S002

LABELING

Labeling: Original
NDA No: 19-386 Rec'd. July 15, 19
Reviewed by: K. Gangwani
Aug 1, 1988

APPROVED
AUG 15 1988

BREVIBLOC® INJECTION
(esmolol hydrochloride)

APPROVED
AUG 15 1988

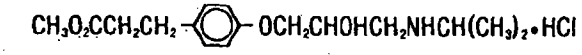
10 mL Ampul — 2.5 g: NOT FOR DIRECT INTRAVENOUS INJECTION. AMPUL MUST BE DILUTED PRIOR TO ITS INFUSION [SEE DOSAGE AND ADMINISTRATION SECTION].

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® (esmolol HCl) INJECTION 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 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® (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® 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® (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 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 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 and 24 hours at 150 mcg/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® (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 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, 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 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) 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. 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).

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 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.

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 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® (esmolol HCl) in almost 400 clinical trial patients with supraventricular tachycardia. In addition, over 600 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 11%, about half of whom 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. 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 (past 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.

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 of BREVIBLOC® of 5000-6250 mcg/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.

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, 3-6 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 or less. The average effective dosage of BREVIBLOC® was approximately 100-115 mcg/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® (esmolol HCl) 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 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 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® (esmolol HCl) 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 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®, specific treatment may also be considered. (See Overdosage.)

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 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

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.

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. The average effective dosage is approximately 100 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 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 the 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.

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

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 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® 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.

Compatibility with Commonly Used Intravenous Fluids

BREVIBLOC® (esmolol HCl) 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 0094-0015-71, 100 mg — 10 mL vial, Box of 20

NDC 0094-0025-18, 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.

Du Pont Pharmaceuticals
E. I. du Pont de Nemours and Company
Wilmington, Delaware 19898

Date: May, 1988

A43049

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-386/S001 and S002

MEDICAL REVIEW

JUL 19 1988

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA: 19386

Name of Drug: Brevibloc (esmolol)
Type of Submission: Revision of labeling

Sponsor: Du Pont Critical Care

Date of Submission: 07/12/88
Date Received by FDA: 07/15/88
Date of Assignment: 07/15/88
Date of Review: 07/19/88

Reviewer: Shaw T. Chen, M.D./HFN-110

A. Resume:

The sponsor has received recently more reports of accidental overdose with esmolol due to error in dilution. The following changes of the labeling text are now proposed to update the information on overdosage (the usual recommended dose is 500 mcg/kg/min) and to emphasize proper method of dilution and preparation of drug:

For the Section on Overdosage:

> A few cases of massive accidental overdosage of BREVIBLOC® (esmolol HCl) have occurred due to errors in dilution. These intravenous bolus doses of BREVIBLOC® of 5000-6250 mcg/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.
>
> Symptomatic Hypotension: Intravenous administration of fluids and/or pressor agents.

For the Section on Dosage and Administration:

> 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).

B. Comments:

In view of the increased incidence of massive overdose, the labeling text concerning esmolol overdose and preparation needs to be changed. However, the proposed revision failed to include the safety data from one additional case reported recently.

The patient, a 49 year old female, was given 250-375 mg (5000-7500 mcg/kg for 50 kg body weight) of Brevibloc for hypertension after colonoscopy and polyp removal. Patient developed apnea, third degree heart block and severe hypotension. Normal sinus rhythm returned briefly after CPR and cardioversion was later required for ventricular arrhythmia. Patient was on the respirator for five days and still not really responsive at the last report. Form 1639 of the case is attached.

The above case indicates that massive overdose of Brevibloc can cause, in addition to severe hypotension

As it was also suggested in this case, the management of massive esmolol overdose may be more difficult than that described in the labeling revision. Thus the prevention of accidental overdosage with more strong warning is very important.

C. Recommendation:

Further revision of the labeling text to incorporate the above information is recommended.

Shaw T. Chen, M.D.,Ph.D., HFN-110

cc:
ORIG: NDA-19386
HFN-110
HFN-110//CSO
HFN-110/SChen/07/19/88

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CHEMISTRY REVIEW(S)

171

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION	2. NDA NUMBER
HFN-110	19-386

3. NAME AND ADDRESS OF APPLICANT *(City and State)*

DuPont Critical Care Inc.
Waukegan, IL 60085

4. AF NUMBER

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
SLF-000	1/12/87
SCP-001	1/21/87

6. NAME OF DRUG	7. NONPROPRIETARY NAME
BREVIBLOC	esmolol hydrochloride

8. SUPPLEMENT(S) PROVIDES FOR:

SLF-001: Final Printed Labeling.

SCP-002: 10 mL Single Dose Vial.

9. AMENDMENTS AND OTHER (Reports, etc.) DATES

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF(S)
Anti-adrenergic (B-receptor)	☒ Rx ☐ OTC	

13. DOSAGE FORM (S)	14. POTENCY (Iso)
Intravenous	2.5 g/10 mL

15. CHEMICAL NAME AND STRUCTURE

Refer to previous reviews

16. RECORDS AND REPORTS

CURRENT ☒ YES ☐ NO

REVIEWED ☒ YES ☐ NO

17. COMMENTS

SLF-001: The final printed labels for the ampules, unit carton and shelf carton and the package insert are submitted. They are all satisfactory as far as the technical aspects are concerned.

SCP-002: Manufacturing and controls information for 10 mL single dose vials is provided. The drug solution is identical to the previously approved ampule dosage form. The container/closure system for the vials consists of USP type I glass vials [redacted] and an aluminum flip-off over seal. Adequate information is provided on the characteristics of the stopper. A technical report is included to show that the stoppers are compatible with a veriety of solutions.

Stability protocol and standard statements of commitment are included and they are identical to those of the ampul dosage form. Stability data is provided for the drug stored in the vials (both upright and inverted) under normal and accelerated conditions. The stability profiles are similar to the ampul dosage forms. The assigned expiry dating period of [redacted] is reasonable for the vials.
Draft labeling is included. Changes were made in the technical portions only. Satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

S-001: NAI

S-002: AE

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
B Rao Vishnuvajjala	B Rao Vishnuvajjala	3/2/87

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FORM FDA 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED. 1

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ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: FEB 24 1989

FROM: Sandra Benton, Technical Information Assistant
Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: NDA 19-386/S-001, Brevibloc (esmolol hydrochloride) Injection

TO: File

The firm submitted a supplement to their new drug application dated January 21, 1987. The supplement was assigned S-001; it provided for a 10 mL single dose vial of Brevibloc (esmolol hydrochloride) Injection. An approvable letter was issued August 4, 1987.

In their letter dated September 17, 1987, the firm submitted another supplement for a new dosage form of Brevibloc (esmolol HCl) consisting of a 10 mL single use vial containing esmolol HCl 10 mg/mL (total of 100 mg) suitable for direct intravenous injection. This supplement was assigned S-004 and was amended with the letters dated November 19, 1987, March 20 and June 17 and 30, 1988. S-004 was approved August 15, 1988.

Therefore, the June 30, 1988 amendment to the September 17, 1987 submission containing final printed labeling should also be coded as AF for S-001. For administrative purposes, this notation has been added to our copies of the letter and the COMIS; approval action for S-001 is the August 15, 1988 letter.

cc
Orig.
HFD-110
HFD-110/CSO
HFD-110/SBenton/2/22/89;2/24/89/1989S
R/D: NMorgenstern/2/23/89

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: OCT 19 1988

FROM: Sandra Benton, Technical Information Assistant
Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: NDA 19-386/S-002, Brevibloc (esmolol hydrochloride) Injection

TO: File

In their submission dated March 3, 1987, the firm proposed the following changes to the package insert:

1. "Dextrose (5%) in Lactated Ringer's Injection" added to the list of intravenous fluids into which Brevibloc may be diluted.

2. The phrase, "This specific dosage and administration regimen has not been studied intraoperatively and, because of the time required for titration, may not be optimal for intraoperative use" was inserted as a fourth paragraph under DOSAGE AND ADMINISTRATION - Supraventricular Tachycardia.

This supplement was assigned S-002; an approvable letter was issued August 4, 1987.

A SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED submission dated July 12, 1988 was assigned S-006. The supplement provided for final printed labeling revised to strengthen the Overdosage and Dosage and Administration sections. This labeling also contained the changes proposed in S-002. S-006 was approved August 15, 1988.

Therefore, the July 12, 1988 submission should also have been coded as AE for S-002. For administrative purposes, this notation has been added to our copies of the letter and the COMIS; approval action for S-002 is the August 15, 1988 letter.

cc
Orig.
HFD-110
HFD-110/CSO
HFD-110/NMorgenstern
HFD-110/SBenton/10/17/88;10/19/88/1430S
R/D: NMorgenstern/10/18/88