CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-386/S007

Trade Name: Brevibloc

Generic Name: Esmolol HCl Injection

Sponsor: Dupont Critical Care Inc.

Approval Date: May 11, 1989

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/S007

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-998/S038

APPROVAL LETTER

MAY 11 1989

NDA 19-386/S-007

Dupont Critical Care, Inc.
Attention: Ms. Sharon L. Richter
1600 Waukegan Road
Waukegan, IL 60085

Dear Ms. Richter:

We acknowledge the receipt on April 11, 1989 of your April 6, 1989 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Brevibloc (esmolol HCl) Injection.

The supplemental application provides for the addition of the 1 gram/10 ml ampul dosage strength as well as revised Shelf Tray labels and printed Package Insert. We note that this dosage strength was included in the original NDA but at the time of approval, you did not wish to market it.

We have completed the review of this supplemental application and it is approved. Our letter of December 31, 1986 detailed the conditions relating to the approval of this application.

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

Should you have any questions, please contact:

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

Sincerely yours,

RZ 5/11/89

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/ZMcDonald/4/21/89;4/24/89
sb/4/24/89;4/28/89;5/2/89/22465 Jm 5/2/89
R/D: RWalters/4/25/89
SOhen/4/25/89
MMorgenstern/4/26/89;4/28/89 mam 5/4/89

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-386/S007

LABELING

Labeling: Original
NDA No: 19386 Rec'd. April 11, 1989
Reviewed by: Zelda DeConna

APPROVED
MAY 11 1989

NDA 19-386

BREVIBLOC® INJECTION

(ESMOLOL HYDROCHLORIDE)

INSERT - A43113

new

DUPONT BREVIBLOC® INJECTION
(esmolol hydrochloride)

10 mL Ampul — Each mL contains 2.5 g: NOT FOR DIRECT INTRAVENOUS INJECTION AND MUST BE DILUTED PRIOR TO ITS INFUSION (SEE DOSAGE AND ADMINISTRATION SECTION).

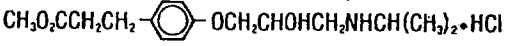
10 mL Single Dose Vial — 100 mg

APPROVED
MAY 11 1989

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 formlua $C_{16}H_{26}NO_4Cl$ 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.

[redacted]

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.

Labeling: Original

NDA No: 19586 Rec'd. April 11, 1989

NDA 19-286

APPROVED

MAY 11 1989

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).

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 given with warfarin, but this is not likely to be clinically important.

Labeling: Original
NDA No: 19386 Rec'd. April 11
Reviewed by: Zelda Nelson

APPROVED

MAY 11 1989

NDA 19-386

BREVIBLOC® INJECTION

(ESMOLOL HYDROCHLORIDE)

INSERT - A43113

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 (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.

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 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.

Labeling: Original
NDA No: 19386 Rec'd. April 11, 19
Reviewed by: Zelda DeSouza

APPROVED
MAY 11 1989

NDA 19-386

BREVIBLOC® INJECTION

DOSAGE AND ADMINISTRATION

1 g and 2.5 g AMPUL

THE 1 g AND 2.5 g AMPULS ARE NOT FOR DIRECT INTRAVENOUS INJECTION. THESE DOSAGE FORMS ARE CONCENTRATED, POTENT DRUGS WHICH MUST BE DILUTED PRIOR TO 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:

1 g AMPUL — Aseptically prepare a 10 mg/mL infusion by adding five 1 g ampuls to a 500 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.

2.5 g AMPUL — Aseptically prepare a 10 mg/mL infusion, by adding two 2.5 g ampuls to a 500 mL container, or one 2.5 g ampul to a 250 mL container, of a compatible intravenous solution listed below. (Remove overage prior to dilution as appropriate). This yields a final concentration of 10 mg/mL.

The diluted solution is stable for at least 24 hours at room temperature. Note: Concentrations of BREVIBLOC® greater than 10 mg/mL are likely to produce irritation on continued infusion (see Precautions). BREVIBLOC® has, however, been well tolerated when administered via a central vein.

100 mg VIAL

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

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 0056-0015-71, 100 mg — 10 mL vial, Box of 20
[redacted]
NDC 0056-0025-18, 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.

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

NDA 19-386

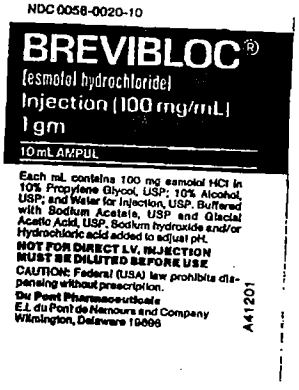
BREVIBLOC® INJECTION

(ESMOLOL HYDROCHLORIDE)

1 GRAM AMPUL LABEL - A41201

MAY 11 1989

APPROVED



NDA 19-386

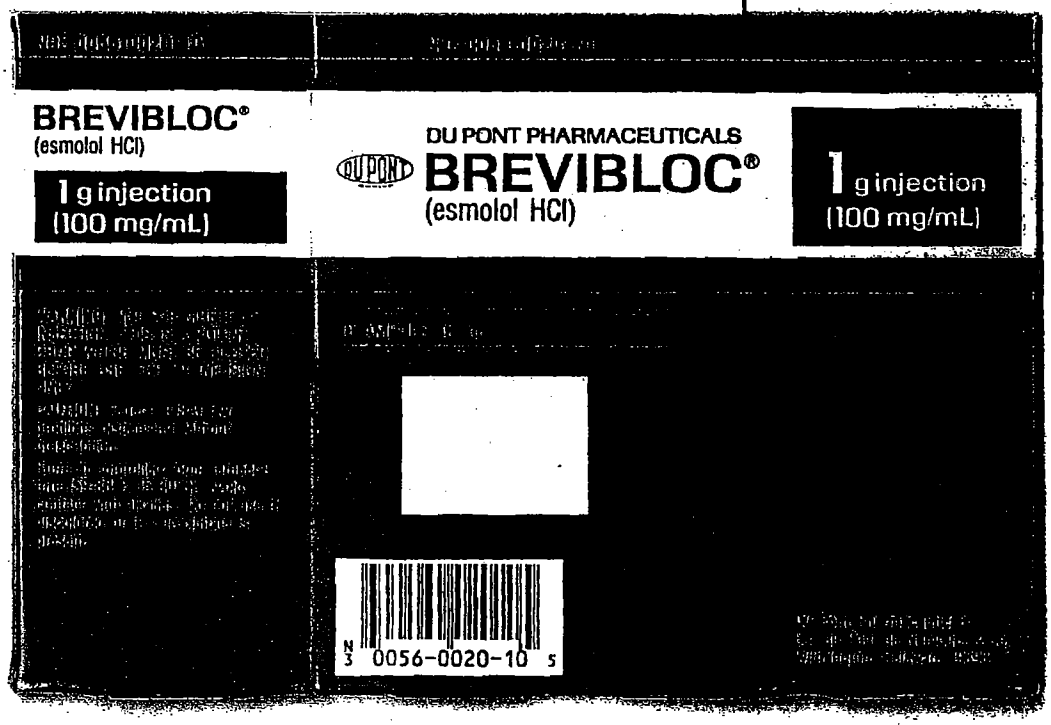
BREVIBLOC® INJECTION

(ESMOLOL HYDROCHLORIDE)

1 GRAM AMPUL SHELF TRAY - A57049

APPROVED

MAY 11 1989



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-386/S007

CHEMISTRY REVIEW(S)

APR 18 1989

CHEMIST'S REVIEW	1. Organization HFD - 110	2. NDA Number 19-386
3. Name and Address of Applicant (City & State) DuPont Critical Care 1600 Waukegan Road Waukegan, IL 60085		4. AF Number 5. Supplement(s) Number(s) ! Date(s)
6. Name of Drug Brevibloc	7. Nonproprietary Name Esmolol Hydrochloride	S-007 (LF) ! 4/6/89
8. Supplement(s) Provides For: Labels and labeling for 1 g ampul, in response to approvable letter of December 31, 1986.		9. Amendments and Other (Reports, etc.) Dates
10. Pharmacological Category Anti-adrenergic (ß-receptor)	11. How Dispensed /X/ RX / / OTC	12. Related IND/NDA/DMF(s)
13. Dosage Form(s) Injection	14. Potency(ies) 100 mg/mL, 250 mg/mL 10 mg/mL	
15. Chemical Name and Structure		16. Records & Reports Current ____Yes ____No Reviewed ____Yes ____No

17. Comments

Labeling included is for the dosage of 100 mg/mL in 10 mL ampul or 1 g esmolol hydrochloride/ampul. Ampul label and tray label do not have expiration date or lot number. Expiration date and lot no. are stamped on at the time of the manufacture (CSO called for the information).
Package insert - A43113, Rev. March 1989 - satisfactory for DESCRIPTION and HOW SUPPLIED sections.

18. Conclusions and Recommendations

Insert is satisfactory for DESCRIPTION and HOW SUPPLIED sections. Ampul and shell tray labels - satisfactory. Expiration date and lot number is stamped on at the time of the manufacture.

4/18/89

19. REVIEWER		
Name Danute G. Cunningham	Signature Danute G. Cunningham	Date Completed April 18, 1989
Distribution	/X/ Original Jacket	/ /Reviewer / /Div. File

Wang 0288c / / CSO (McDonald)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-386/S007

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CSO Review of Final Printed Labeling MAY 11 1989
NDA 19-386/S-007

Date of submission: April 6, 1989

Date of Review: April 22, 1989

Applicant Name: Dupont Critical Care, Inc.

Product Name: Brevibloc (esmolol HCL) Injection

Evaluation:

This supplement provides for the addition of the 1 gram strength to the Ampul, Shelf Tray and Package Insert labels. The original NDA provided for this strength in the Manufacturing and Controls section (Vol. 2.1) submitted on November 30, 1984. Dupont has not wished to market this strength until now.

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

Ms. Cunningham's review found the DESCRIPTION and HOW SUPPLIED sections satisfactory.

Recommendation:
An approval letter should issue for S-007 as set forth under 21 CFR 314.70 (b) (3). [Any change in labeling.]

Zelda McDonald

Zelda McDonald, CSO

cc: Orig. NDA
HFD-110
HFD-111/McDonald
HFD-111/Morgenstern