CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-386/S009

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-386/S009

Trade Name: Brevibloc Injection

Generic Name: Esmolol Hydrochloride

Sponsor: Du Pont Merck Pharmaceutical Company

Approval Date: October 21, 1991

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/S009

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-386/S-009

OCT 21 1991

The Du Pont Merck Pharmaceutical Company
Attention: Mr. Edward B. Adams
Barley Mill Plaza, P27/2368
Wilmington, DE 19880-0027

Dear Mr. Adams:

Please refer to your December 15, 1989 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Brevibloc (esmolol hydrochloride) Injection.

We also acknowledge receipt of your amendment dated September 25, 1991.

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

1. The statement, above the **DESCRIPTION** section, that the ampul is not for direct intravenous injection has been made more prominent.

2. Under the **DESCRIPTION** section, the following paragraph has been removed:

> 1 g. 10 mL Ampul - Each mL contains 100 mg esmolol HCl in 10% Propylene Glycol, USP, 10% alcohol, USP and Water for injection, USP; buffered with 6.8 mg Sodium Acetate, USP, and 0.00286 mL Glacial Acetic Acid, USP Sodium hydroxide and/or hydrochloric acid added, as necessary, to adjust pH to 3.5-5.5.

3. Under the **DESCRIPTION** section, the phrase, "For intravenous infusion after dilution." has been deleted from the end of the fifth paragraph.

4. Under the **WARNINGS/Cardiac Failure** section, the wording after the first two sentences has been changed to read:

> At the first sign or symptom of impending cardiac failure, BREVIBLOC should be withdrawn. Although withdrawal may be sufficient because of the short elimination half-life of BREVIBLOC, specific treatment may also be considered. (see **OVERDOSAGE**.) The use of Brevibloc for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the

> myocardium. Despite the rapid onset and offset of Brevibloc's effects, several cases of death have been reported in complex clinical states where Brevibloc was presumably being used to control ventricular rate.

5. Under the **PRECAUTIONS/General** subsection, the phrase ". . . and thrombophlebitis" has been replace with ". . . including thrombophlebitis" in the first sentence of the first paragraph; the sentence, "Extravasation of 20 mg/mL may lead to a serious local reaction and possible skin necrosis" has been added; the phrase, "or infusion into small veins or through a butterfly catheter" has been added to the last sentence; and the following paragraph has been added at the end of this subsection:

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

6. The wording about anaphylactic reactions has been move to the **PRECAUTIONS/Drug Interactions** subsection. In addition, the following paragraph has been added to this subsection:

> Caution should be exercised when considering the use of BREVIBLOC and Verapamil in patients with depressed myocardial function. Fatal cardiac arrests have occurred in patients receiving both drugs. Additionally, BREVIBLOC should not be used to control supraventricular tachycardia in the presence of agents which are vasoconstrictive and inotropic such as dopamine, epinephrine, and norepinephrine because of the danger of blocking cardiac contractility when systemic vascular resistance is high.

7. Under the **ADVERSE REACTIONS/Central Nervous System** subsection, the sentence, "One brief (30 second) episode of grand mal seizure has been reported" has been replaced with the sentence, "Seizures were also reported in less than 1% of patients, with one death."

8. Under the **ADVERSE REACTIONS/Skin (Infusion Site)** subsection, the phrase, "thrombophlebitis, and local skin necrosis from extravasation" has been added to the list of adverse reactions reported in less than 1% of patients.

9. Under the **DOSAGE AND ADMINISTRATION/Dilution** subsection the following paragraph has been deleted:

> 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.

10. Under the **DOSAGE AND ADMINISTRATION/100 mg vial** subsection, the sentence, "When using the 100 mg vial, a loading dose of 0.5 mg/kg/min for a 70 kg patient would be 3.5 mL." has been added.

11. Under the **DOSAGE AND ADMINISTRATION/Supraventricular Tachycardia** subsection, the second and third paragraphs have been revised and a table has been added as follows:

> To initiate treatment of a patient with supraventricular tachycardia, administer a loading infusion of 500 mcg/kg/min (0.5 mg/kg/min) over one minute followed by a four-minute maintenance infusion of 50 mcg/kg/min (0.05 mg/kg/min). If an adequate therapeutic effect is observed over the five minutes of drug adminstration, maintain the maintenance infusion dosage with periodic adjustments up or down as needed. If an adequate therapeutic effect is not observed, the same loading dosage is repeated over one minute followed by an increased maintenance rate infusion of 100 mcg/kg/min (0.1 mg/kg/min).
>
> Continue titration procedure as above, repeating the original loading infusion of 500 mcg/kg/min (0.5 mg/kg/min) over 1 minute, but increasing the maintenance infusion rate over the subsequent four minutes by 50 mcg/kg/min (0.05 mg/kg/min) increments. As the desired heart rate or blood pressure is approached, omit subsequent loading doses and titrate the maintenance dosage up or down to endpoint. Also, if desired, increase the interval between steps from 5 to 10 minutes.

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

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

12. Under the **DOSAGE AND ADMINISTRATION/Supraventricular Tachycardia** subsection, the phrase, "and caution should be taken to prevent extravasation" has been added to the sixth paragraph.

13. Under the **HOW SUPPLIED** section the NDC labeler code has been revised from 0094 to 0590, reference to the 1 g ampul has been deleted, and the company signature has been updated to reflect the Manati, Puerto Rico name and address.

14. Dosages have been expressed as both mcg/kg/min and mg/kg/min (instead of mcg/kg/min only) throughout the insert.

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

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

Sincerely yours,

RJL 10/18/91

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~~
HFC-130/JAllen
HFD-110
HFD-110/CSO
HFD-80
HFD-232 (with labeling)
HFD-110/ZMcDonald/10/11/91;10/15/91 ZM 10/17/91
sb/10/15/91;10/17/91
R/D: RWolters/10/16/91
SChen
NMorgenstern/10/15/91

Approval Date: December 31, 1986

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-386/S009

LABELING

Labeling: Working Copy
NDA No: 19-386 Rec'd. 9-30-91
Reviewed by: Zella McDonald
10/11/91

BREVIBLOC® INJECTION
(esmolol hydrochloride)

10 mL Ampul—2.5 g

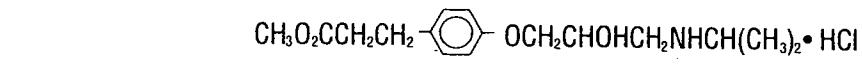
10 mL Single Dose Vial—100 mg

Not for direct intravenous injection. Ampul must be diluted prior to its infusion—see 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:



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. —

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

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

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

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

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

Pharmacodynamics

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

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

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

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

INDICATIONS AND USAGE
Supraventricular Tachycardia
BREVIBLOC® (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 (0.2 mg/kg/min) are not recommended. Patients should be closely monitored, especially if pretreatment blood pressure is low. Decrease of dose or termination of infusion reverses hypotension, usually within 30 minutes.

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

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

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

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

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

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

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

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

When digoxin and BREVIBLOC® (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, BREVI-

BLOC® should be titrated with caution in patients being treated concurrently with digoxin, morphine, succinylcholine or warfarin.

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

Caution should be exercised when considering the use of BREVIBLOC® and Verapamil in patients with depressed myocardial function. Fatal cardiac arrests have occurred in patients receiving both drugs. Additionally, BREVIBLOC® should not be used to control supraventricular tachycardia in the presence of agents which are vasoconstrictive and inotropic such as dopamine, epinephrine, and norepinephrine because of the danger of blocking cardiac contractility when systemic vascular resistance is high.

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

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

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. Seizures were also reported in less than 1% of patients, with one death.

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

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

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

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

OVERDOSAGE

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

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

Bradycardia: Intravenous administration of atropine or another anticholinergic drug.

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

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

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

DOSAGE AND ADMINISTRATION

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

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

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

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

Supraventricular Tachycardia

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

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

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

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

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

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

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

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

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

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

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

The dosage of BREVIBLOC® 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 0590-0015-71, 100 mg — 10 mL vial, Box of 20

NDC 0590-0025-18, 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
Du Pont Merck Pharma
P.O. Box 963
Manati, Puerto Rico 00674

DUPONT

6224-2/Rev. Aug., 1991

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-386/S009

MEDICAL REVIEW

DEC 28 [illegible]

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA: 19,386
Name of Drug: Brevibloc (esmolol)
Type of Submission: Labeling Revision
Sponsor: Du Pont

Date of Submission: 12/15/89
Date Received by FDA: 12/20/89
Date of Assignment: 12/26/89
Date of Review: 12/27/89
Reviewer: Shaw T. Chen, M.D.

A. Resume:

The sponsor submitted a supplement to change the labeling for Brevibloc, as requested by the Agency. The labeling revision addressed the following two adverse experiences.

1. Class change for all beta blockers regarding the risk of aggravated anaphylactic reaction in susceptible patients. The language proposed by the Agency was accepted by the sponsor without modification.

2. The risk of serious and fatal cardiac arrest in patients received esmolol. As highlighted in the attached draft, possible interaction with verapamil was added to the sections of ——— and PRECAUTIONS.

B. Comments:

The proposed labeling for class warning of anaphylaxis was appropriate. However, the changes regarding cardiac arrest was inadequate.

As summarized in previous Medical Officer's Report, prior therapy with verapamil was documented in 6 of the ten cases reviewed and drug interaction was not evident in other patients. Concurrent therapy was also unknown in two additional cases of cardiac arrest (89029, 89030) submitted after the request for labeling change was sent on 11/08/89. Thus drug interaction with verapamil may not be the only complicating risk for patients receiving esmolol.

While many of the twelve patients reported to date had complicated underlying conditions, others were relatively young and without documented heart failure at the time of various procedures/surgeries (5 patients aged below 40). Despite that no other specific risk factors could be identified, the labeling revision should include a broader warning against life threatening or fatal hemodynamic decompensation in patients who had not

received verapamil.

C. Recommendation:

Further revision of the labeling regarding the risk of cardiac arrest is recommended as follows:

Under _____ the proposed statements should be changed to:

_____

The Statements on Drug Interactions in the PRECAUTIONS should be retained.

Shaw T. Chen, M.D.,Ph.D.

cc:
ORIG: NDA-19,386
HFD-110
HFD-110/CSO
HFD-110/SChen/12/28/89

FEB 7 1991

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA: 19-386
Name of Drug: Brevibloc (esmolol)
Type of Submission: Labeling Revision
Sponsor: Du Pont-Merck

Dates of
Submission: 01/24/91
Receipt: 01/31/91
Assignment: 02/04/91
Review: 02/04/91

Reviewer: Shaw T. Chen, M.D.

A. Resume:

A draft labeling was submitted, the changes related to the warning against severe cardiac decompensation and risk of anaphylactic reaction are now in agreement with the Agency's request. However, the sponsor changed two words in the WARNING/Cardiac failure section:

1. "The use of Brevibloc ..... should be undertaken [redacted] caution." was changed to "..... with caution."
2. "Brevibloc was presumably being used [redacted] to control ventricular rate." was changed to ".....to control ventricular [redacted]

Other labeling changes include addition of skin necrosis due to infiltration, rewording of seizures in the CNS section, and a revised dosage/administration section.

B. Comments:

The second change is not acceptable; Brevibloc is approved only for the treatment of supraventricular tachycardia (SVT), not [redacted] In addition, [redacted]

The word [redacted] was considered redundant in the WARNING Section. Its deletion is less objectionable. Other revisions in the draft labeling were acceptable.

C. Recommendation:

The statement [redacted] should remain unchanged. The rest of draft labeling should be approved.

Shaw T. Chen, M.D.,Ph.D.

cc:
ORIG: NDA-19-386
HFD-110
HFD-110/CSO
HFD-110/SChen/02/04/91

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-386/S009

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-386/S-009

APR 12 1991

The Du Pont Merck Pharmaceutical Company
Attention: Karen Veronich, Ph.D.
P.O. Box 80027
Wilmington, DE 19880-0027

Dear Dr. Veronich:

Please refer to your December 15, 1989 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Brevibloc (esmolol hydrochloride) Injection.

We also acknowledge receipt of your amendments dated January 24, 1991 and February 20, 1991.

The supplemental application provides for draft labeling revised as follows:

January 24, 1991 submission

1. Under the **WARNINGS/Cardiac Failure** section, the wording after the first two sentences has been changed to read:

> At the first sign or symptom of impending cardiac failure, BREVIBLOC should be withdrawn. Although withdrawal may be sufficient because of the short elimination half-life of BREVIBLOC, specific treatment may also be considered. (see **OVERDOSAGE.**) The use of Brevibloc for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium. Despite the rapid onset and offset of Brevibloc, several cases of death have been reported in complex clinical states where Brevibloc was presumably being used to control ventricular ———

2. Under the **PRECAUTIONS/General** subsection, the phrase "...and thrombophlebitis" has been replace with "...including thrombophlebitis" in the first sentence of the first paragraph and the following sentence has been added:

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

3. The wording about anaphylactic reactions has been move to the **PRECAUTIONS/Drug Interactions** subsection. In addition, the following paragraph has been added to this subsection:

> Caution should be exercised when considering the use of BREVIBLOC and Verapamil in patients with depressed myocardial function. Fatal cardiac arrests have occurred in patients receiving both drugs. Additionally, BREVIBLOC should not be used to control supraventricular tachycardia in the presence of agents which are vasoconstrictive and inotropic such as dopamine, epinephrine, and norepinephrine because of the danger of blocking cardiac contractility when systemic vascular resistance is high.

4. Under the **ADVERSE REACTIONS/Central Nervous System** subsection, the following sentence has been added:

> Seizures were also reported in less than 1% of patients, with one death.

5. Under the **DOSAGE AND ADMINISTRATION/100 mg vial** subsection, the following sentence has been added:

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

6. Under the **DOSAGE AND ADMINISTRATION/Supraventricular Tachycardia** subsection, the second and third paragraphs have been revised and a table has been added as follows:

> To initiate treatment of a patient with supraventricular tachycardia, administer a loading infusion of 500 mcg/kg/min (0.5 mg/kg/min) over one minute followed by a four-minute maintenance infusion of 50 mcg/kg/min (0.5 mg/kg/min). If an adequate therapeutic effect is observed over the five minutes of

drug adminstration, maintain the maintenance infusion dosage with periodic adjustments up or down as needed. If an adequate therapeutic effect is not observed, the same loading dosage is repeated over one minute followed by an increased maintenance rate infusion of 100 mcg/kg/min (.1 mg/kg/min).

Continue titration procedure as above, repeating the original loading infusion of 500 mcg/kg/min (.5 mg/kg/min) over 1 minute, but increasing the maintenance infusion rate over the subsequent four minutes by 50 mcg/kg/min (.05 mg/kg/min) increments. As the desired heart rate or blood pressure is approached, omit subsequent loading doses and titrate the maintenance dosage up or down to endpoint. Also, if desire, increase the interval between steps from 5 to 10 minutes.

Time	Loading Dose (Over 1 minute)		Maintenance Dosage (over 4 minutes)	
(Minutes)	mcg/kg/min	mg/kg/min	mcg/kg/min	mg/kg/min
0-1	500	.5		
1-5			50	.05
5-6	500	.5		
6-10			100	.1
10-11	500	.5		
11-15			150	.15
15-16	*	*		
16-20			*200	*.2
20-(24 hrs.)			Maintenance dose titrated to heart rate or other clinical endpoint.	

*As the desired heart rate or endpoint is approached, the loading infusion may be omitted and the maintenance infusion titrated to 300 mcg/kg/min (.3 mg/kg/min) or downward as appropriate. Maintenance dosages above 200 mcg/kg/min (.2 mg/kg/min) have not been shown to have significantly increased benefits. The interval between titration steps may be increased.

7. The statement that the ampul is not for direct intravenous injection has been made more prominent and dosages have been expressed as both mcg/kg/min and mg/kg/min throughout the insert.

February 20, 1991 submission

1. Under the **DESCRIPTION** section, the following phrase has been deleted from the end of the fifth paragraph, "For intravenous infusion after dilution."

2. Under the **PRECAUTIONS/General** subsection, first paragraph, the sentence, "Extravasation of 20 mg/mL may lead to a serious local reaction and possible skin necrosis," has been added and the phrase, "or infusion into small veins or through a butterfly catheter" has been added to the last sentence.

3. Under the **ADVERSE REACTIONS/Skin (Infusion Site)** subsection, the phrase, "thrombophlebitis, and local skin necrosis from extravasation" has been added to the list of adverse reactions reported in less than 1% of patients.

4. Under the **DOSAGE AND ADMINISTRATION/Supraventricular Tachycardia** subsection, the phrase, "and caution should be taken to prevent extravasation" has been added to the sixth paragraph.

5. Under the **HOW SUPPLIED** section the NDC labeler code has been revised from 0094 to 0590, and the company signature has been updated to reflect the Manati, Puerto Rico name and address.

We have completed the review of this supplemental application as submitted with draft labeling. Before the supplement may be approved, however, it will be necessary for you to submit final printed labeling. The labeling should be identical in content to the draft labeling, except that the word "rate" should be substituted for the word ———— in the last sentence of the **WARNINGS/Cardiac Failure** subsection, and all numerical values for expressing mg/kg/min should be consistent e.g., 0.5 mg/kg/min instead of .5 sometimes and 0.5 at other times. In addition, all previous revisions as reflected in the most recently approved package insert must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

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 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 this supplemental 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 this supplemental application.

Should you have any questions, please contact:

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

Sincerely yours,

RK 4/12/91

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
HFC-130/JAllen
HFD-110
HFD-110/CSO
HFD-83
HFD-110/ZMcDonald/3/26/91
sb/4/10/91;4/11/91
R/D: RWolters/4/1/91
CResnick/4/1/91
SChen/4/8/91
NMorgenstern;4/10/91

APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-386/S009

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CSO Review of Final Printed Labeling
NDA 19-386/S-009

OCT 21 1991

Date of Submission: September 25, 1991

Date of Review: October 10, 1991

Applicant Name: The Du Pont Merck Pharmaceutical Company

Product Name: Brevibloc (esmolol hydrochloride) Injection

Background:
Supplement 9 was submitted with draft labeling on December 15, 1989. We reviewed the labeling and issued an approvable letter on June 7, 1990 with labeling changes. An amendment dated February 20, 1991 was submitted that referred to "Changes Being Effected" that had been incorporated in this labeling but not cited at the time of submission. We issued an approvable letter on April 12, 1991 for the original submission and the amendment.

Evaluation:
This submission provides for final printed labeling in accordance with our approvable letter dated April 12, 1991. The changes are as follows:

1. The statement, above the DESCRIPTION section, that the ampul is not for direct intravenous injection has been made more prominent.

2. Under the DESCRIPTION section, the following paragraph has been removed:

1 g. 10 mL Ampul - Each mL contains 100 mg esmolol HCl in 10% Propylene Glycol, USP, 10% alcohol, USP and Water for injection, USP; buffered with 6.8 mg Sodium Acetate, USP, and 0.00286 mL Glacial Acetic Acid, USP Sodium hydroxide and/or hydrochloric acid added, as necessary, to adjust pH to 3.5-5.5.

3. Under the DESCRIPTION section, the phrase, "For intravenous infusion after dilution." has been deleted from the end of the fifth paragraph.

4. Under the WARNINGS/Cardiac Failure section, the wording after the first two sentences has been changed to read: "At the first sign or symptom of impending cardiac failure, BREVIBLOC should be withdrawn. Although withdrawal may be sufficient because of the short elimination half-life of BREVIBLOC, specific treatment may also be considered. (see OVERDOSAGE.) The use of Brevibloc for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium. Despite the rapid onset and offset of Brevibloc's effects, several cases of death have been reported in complex clinical states where Brevibloc was presumably being used to control ventricular rate.

5. Under the PRECAUTIONS/General subsection, the phrase "...and thrombophlebitis" has been replace with "...including thrombophlebitis" in the first sentence of the first paragraph; the sentence, "Extravasation of 20 mg/mL may lead to a serious local reaction and possible skin necrosis" has been added; the phrase, "or infusion into small veins or through a butterfly catheter" has been added to the last sentence; and the following paragraph has been added at the

end of this subsection:

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

6. The wording about anaphylactic reactions has been move to the PRECAUTIONS/Drug Interactions subsection. In addition, the following paragraph has been added to this subsection:

Caution should be exercised when considering the use of BREVIBLOC and Verapamil in patients with depressed myocardial function. Fatal cardiac arrests have occurred in patients receiving both drugs. Additionally, BREVIBLOC should not be used to control supraventricular tachycardia in the presence of agents which are vasoconstrictive and inotropic such as dopamine, epinephrine, and norepinephrine because of the danger of blocking cardiac contractility when systemic vascular resistance is high.

7. Under the ADVERSE REACTIONS/Central Nervous System subsection, the sentence, "One brief (30 second) episode of grand mal seizure has been reported" has been replaced with the sentence, "Seizures were also reported in less than 1% of patients, with one death."

8. Under the ADVERSE REACTIONS/Skin (Infusion Site) subsection, the phrase, "thrombophlebitis, and local skin necrosis from extravasation" has been added to the list of adverse reactions reported in less than 1% of patients.

9. Under the DOSAGE AND ADMINISTRATION/Dilution subsection the following paragraph has been deleted:

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.

10. Under the DOSAGE AND ADMINISTRATION/100 mg vial subsection, the sentence, "When using the 100 mg vial, a loading dose of 0.5 mg/kg/min for a 70 kg patient would be 3.5 mL." has been added.

11. Under the DOSAGE AND ADMINISTRATION/Supraventricular Tachycardia subsection, the second and third paragraphs have been revised and a table has been added as follows:

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

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

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

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

12. Under the DOSAGE AND ADMINISTRATION/Supraventricular Tachycardia subsection, the phrase, "and caution should be taken to prevent extravasation" has been added to the sixth paragraph.

13. Under the HOW SUPPLIED section the NDC labeler code has been revised from 0094 to 0590, reference to the 1 g ampul has been deleted, and the company signature has been updated to reflect the Manati, Puerto Rico name and address.

14. Dosages have been expressed as both mcg/kg/min and mg/kg/min (instead of mcg/kg/min only) throughout the insert.

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

Recommendation:
An approval letter should issue for S-009 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/Benton

APR 12 1991

CSO Review of Draft Labeling
NDA 19-386/S-009

Date of Submission: January 24, 1991 (amendment to original dated December 15, 1989)

Date of Review: March 25, 1991

Applicant Name: The Du Pont Merck Pharmceutical Company

Product Name: Brevibloc (esmolol hydrochloride) Injection

Background:
Supplement 9 was submitted with draft labeling on December 15, 1989. We reviewed the labeling and issued an approvable letter on June 7, 1990 wherein we requested the following changes before the supplement could be approved:

WARNINGS/Cardiac Failure:

The use of Brevibloc for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with ——— caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium. Despite the rapid onset and offset of ——————— several cases of death have been reported in complex clinical states where Brevibloc was presumably being used ———to control ventricular rate.

PRECAUTIONS/Drug Interactions:

Caution should be exercised when considering the use of Brevibloc and verapamil in patients with depressed myocardial function. Fatal cardiac arrests have occurred in patients receiving both drugs.

Evaluation:
This submission is an amendment to supplement 9 with draft labeling. It provides for revisions essentially the same as requested in our letter of June 7, 1990. In addition, the statement that the ampul is not for direct intravenous injection has been made more prominent and dosages have been expressed as both mcg/kg/min and mg/kg/min (instead of mcg/kg/min only) throughout the insert. A section was added to the precautions section regarding sloughing of the skin and necrosis associated with infiltration and extravasation. Rewording regarding seizures listed under ADVERSE REACTIONS/Central Nervous System has been proposed. The DOSAGE AND ADMINISTRATION section has been revised slightly and expanded to include a new table. The changes are as follows:

1. Under the WARNINGS/Cardiac Failure section, the wording after the first two sentences has been changed to read: "At the first sign or symptom of impending cardiac failure, BREVIBLOC should be withdrawn. Although withdrawal may be sufficient because of the short elimination half-life of BREVIBLOC, specific treatment may also be considered. (see OVERDOSAGE.) The use of Brevibloc for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically or is

taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium. Despite the rapid onset and offset of ————————, several cases of death have been reported in complex clinical states where Brevibloc was presumably being used simply to control ventricular ————

2. Under the PRECAUTIONS/General subsection, the phrase "...and thrombophlebitis" has been replace with "...including thrombophlebitis" in the first sentence of the first paragraph and the following sentence has been added:

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

3. The wording about anaphylactic reactions has been move to the PRECAUTIONS/Drug Interactions subsection. In addition, the following paragraph has been added to this subsection:

Caution should be exercised when considering the use of BREVIBLOC and Verapamil in patients with depressed myocardial function. Fatal cardiac arrests have occurred in patients receiving both drugs. Additionally, BREVIBLOC should not be used to control supraventricular tachycardia in the presence of agents which are vasoconstrictive and inotropic such as dopamine, epinephrine, and norepinephrine because of the danger of blocking cardiac contractility when systemic vascular resistance is high.

4. Under the ADVERSE REACTIONS/Central Nervous System subsection, the sentence, "Seizures were also reported in less than 1% of patients, with one death." was added.

5. Under the DOSAGE AND ADMINISTRATION/100 mg vial subsection, the sentence, "When using the 100 mg vial, a loading dose of 0.5 mg/kg/min for a 70 kg patient would be 3.5 mL." has been added.

6. Under the DOSAGE AND ADMINISTRATION/Supraventricular Tachycardia subsection, the second and third paragraphs have been revised and a table has been added as follows:

To initiate treatment of a patient with supraventricular tachycardia, administer a loading infusion of 500 mcg/kg/min (0.5 mg/kg/min). If an adequate therapeutic effect is observed over the five minutes of drug adminstration, maintain the maintenance infusion dosage with periodic adjustments up or down as needed. If an adequate therapeutic effect is not observed, the same loading dosage is repeated over one minute followed by an increased maintenance rate infusion of 100 mcg/kg/min (.1 mg/kg/min).

Continue titration procedure as above, repeating the original loading infusion of 500 mcg/kg/min (.5 mg/kg/min) over 1 minute, but increasing the maintenance infusion rate over the subsequent four minutes by 50 mcg/kg/min (.05 mg/kg/min) increments. As the desired heart rate or blood pressure is approached, omit subsequent loading doses and titrate the maintenance dosage up or down to endpoint. Also, if desire, increase the interval between steps from 5 to 10 minutes.

Time (Minutes)	Loading Dose (Over 1 minute) mcg/kg/min	mg/kg/min	Maintenance Dosage (over 4 minutes) mcg/kg/min	mg/kg/min
0 - 1	500	.5		
1 - 5			50	.05
5 - 6	500	.5		
6 - 10			100	.1
10 - 11	500	.5		
11 - 15			150	.15
15 - 16	*	*		
16 - 20			*200	*.2
20 - (24 hrs.)			Maintenance dose titrated to heart rate or other Clinical endpoint.	

*As the desired heart rate or endpoint is approached, the loading infusion may be omitted and the maintenance infusion titrated to 300 mcg/kg/min (.3 mg/kg/min) or downward as appropriate. Maintenance dosages above 200 mcg/kg/min (.2 mg/kg/min) have not been shown to have significantly increase benefits. the interval between titration steps may be increased.

Dr. Chen reviewed this labeling and recommended that the last sentence of the WARNINGS/Cardiac Failure subsection should end in ".... to control ventricular rate." (as we originally requested) instead of "... to control ventricular———— Substitution of ———— for "rate" was made by the firm.

An amendment dated February 20, 1991 was submitted that referred to "Changes Being Effected" that had been incorporated in this labeling but not cited at the time of submission. They are as follows:

1. Under the DESCRIPTION section, the phrase, "For intravenous infusion after dilution." has been deleted from the end of the fifth paragraph.

2. Under the PRECAUTIONS/General subsection, first paragraph, the sentence, "Extravasation of 20 mg/mL may lead to a serious local reaction and possible skin necrosis." has been added and the phrase, "or infusion into small veins or through a butterfly catheter" has been added to the last sentence.

3. Under the ADVERSE REACTIONS/Skin (Infusion Site) subsection, the phrase, "thrombophlebitis, and local skin necrosis from extravasation" has been added to the list of adverse reactions reported in less than 1% of patients.

4. Under the DOSAGE AND ADMINISTRATION/Supraventricular Tachycardia subsection, the phrase, "and caution should be taken to prevent extravasation" has been added to the sixth paragraph.

5. Under the HOW SUPPLIED section the NDC labeler code has been revised from 0094 to 0590, and the company signature has been updated to reflect the Manati, Puerto Rico name and address.

The only other change from the last approved package insert is that this draft does not have labeling for the 1 gram strength that was approved in our letter of May 11, 1989 for supplement 7.

Recommendation:
An approvable letter should issue for S-009 pending submission of final printed labeling as set forth under 21 CFR 314.70 (b) (3). [Any change in labeling]. The approvable letter should include Dr. Chen's change of the word ———— back to "rate" in the WARNINGS/Cardiac Failure subsection.

Zelda McDonald

Zelda McDonald, CSO

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

RECORD OF TELEPHONE CONVERSATION

APR 12 1991

Date: March 20, 1991
NDA#: 19-386/S-009
Product: Brevibloc (esmolol hydrochloride) Injection
Firm: The Du Pont Merck Pharmaceutical Company
Contact: Karen Veronich
Phone#: 302-892-1983

Dr. Veronich labeled the submission dated February 20, 1991 as "Changes Being Effected" but then referred to the labeling supplement submitted on January 24,1991 in which she "neglected to highlight the changes being effected." I asked her to clarify what the submission actually was because it seemed to me it would be a new supplement. She said this submission should indeed be a new supplement, and the reason she referred to the January 24, 1991 submission is that the changes had been incorporated in that draft labeling, but not mentioned in the January 24, 1991 letter. The changes have already been implemented in their labeling.

I asked Dr. Veronich to submit an amendment referring to S-010 (since that would be the new supplement number) containing the bases for the changes and 12 copies of final printed labeling. In the meantime we would send her an acknowledgement letter requesting same. I also advised her that "Changes Being Effected" labeling should contain only changes to sections of the labeling referred to in 21 CFR 314.70 (c) [Supplements for changes that may be made before FDA approval.] e.g., it should <u>not</u> contain changes to the DESCRIPTION section.

Dr. Veronich agreed with all of the above.

Zelda McDonald

Zelda McDonald, CSO
HFD-110

N.B. We have since decided to make the February 20, 1991 submission and amendment to S-009. I will call Dr. Veronich and inform her of our decision. Zm 3/29/91

NDA 19-386/S-009

JAN 15 1991

E.I. du Pont de Nemours & Co. (Inc.)
Du Pont Pharmaceuticals
Attention: Karen Veronich, Ph.D.
Barley Mill Plaza
Wilmington, DE 19880-0027

Dear Dr. Veronich:

Please refer to your December 15, 1989 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for Brevibloc (esmolol hydrochloride) Injection.

The supplemental application provided for draft labeling revised as described in our June 7, 1990 letter.

We also refer to our letter of June 7, 1990 notifying you that your supplemental application was approvable with additional changes. Your July 3, 1990 correspondence informed us of your intent to file an amendment to your application. A notice of intent to file an amendment constitutes an agreement by you to extend the review period under 21 CFR 314.60.

We have no record that you have filed an amendment fully responsive to our approvable letter. Since 7 months have passed, we will consider this supplemental application withdrawn under 21 CFR 314.120(e) unless you file such an amendment within thirty (30) days. Alternatively, you may wish to withdraw this supplement to your NDA under 21 CFR 314.65. Withdrawal would not prejudice any future resubmission of the supplemental application. You may request that the information in the withdrawn supplemental application be considered in conjunction with any resubmission.

We are concerned about improving our management of NDAs during the review process. Supplemental applications such as this, overburden our document rooms and distort our workload assignments. We, therefore, hope for your cooperation.

Sincerely yours,

Nam 1/15/91

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
~~NWK-DO~~
Original NDA
HFD-110
HFD-110/CSO Zm 1/15/91
HFD-80/DDIR
HFD-110/SBenton/1/15/91/0710

INFORMATION REQUEST

JUN - 7 1990

NDA 19-386/S-009

E.I. Du Pont De Nemours & Co., Inc.
dba Du Pont Pharmaceuticals
Attention: Patrick A. Roche, Ph.D.
Barley Mill Plaza
Wilmington, DE 19898

Dear Dr. Roche:

Please refer to your December 15, 1989 supplemental new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Brevibloc (esmolol hydrochloride).

The supplemental application provides for draft labeling revised as follows:

1. Under the WARNINGS/Cardiac Failure section the sentences:

   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.)

   were changed to read:

   At the first sign or symptom of impending cardiac failure, Brevibloc should be withdrawn. Although withdrawal may be sufficient because of the short elimination half-life of Brevibloc, specific treatment may also be considered. (See Overdosage.)

2. Under the PRECAUTIONS section the following subsection was added:

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

3. Under the PRECAUTIONS/Drug Interactions section the following paragraph was added:

> Caution should be exercised when considering the use of ——— and verapamil in patients with depressed myocardial function, ———

We have completed the review of this supplemental application as submitted with draft labeling. Before this supplement may be approved, however, it will be necessary for you to make changes as follows:

1. Under the WARNINGS/Cardiac Failure section, leave the first two sentences as they are but revise the remainder of the section to read:

> The use of Brevibloc for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with ——— caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium. Despite the rapid onset and offset of ——— several cases of death have been reported in complex clinical states where Brevibloc was presumably being used ——— to control ventricular rate.

2. Add the following to the PRECAUTIONS/Drug Interactions section:

> Caution should be exercised when considering the use of Brevibloc and verapamil in patients with depressed myocardial function. Fatal cardiac arrests have occurred in patients receiving both drugs.

3. Please move the ——— paragraph to the Drug Interactions subsection of the PRECAUTIONS section, a more appropriate location.

The labeling should be essentially identical in content to the draft labeling but should be revised as requested above. In addition, all previous revisions as reflected in the most recently approved package insert must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

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 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 this supplemental 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 this supplemental application.

Should you have any questions, please contact:

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

Sincerely yours,

RJ 6/7/90

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-110/ZMcDonald/1/4/90;4/3/90;4/11/90 ZM 6/7/90
sb/4/4/90;4/9/90;5/4/90/5256S
R/D: RWolters/5/1/90
SChen
NMorgenstern/5/2/90

APPROVABLE

G Buehler for NAM 5/18/90

CSO Review of Draft Labeling
NDA 19-386/S-009

Date of Submission: December 15, 1989

Date of Review: January 2, 1990

Applicant Name: Du Pont De Nemours & Company

Product Name: Brevibloc (esmolol hydrochloride)

Evaluation:
On November 8, 1989 we sent two letters to Du Pont requesting that they submit supplements for labeling changes. One letter asked that Du Pont address the risk of aggravated anaphylactic reaction in susceptible patients taking beta-blockers and the other letter requested a warning of the incidence of serious adverse hemodynamic reactions associated with the use of esmolol, with particular attention to cardiac arrest and fatal outcome. On December 15, 1989 Du Pont submitted draft labeling that provided for the following changes:

Under the WARNINGS/Cardiac Failure section the sentences: **"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.)"** were changed to read: **"At the first sign or symptom of impending cardiac failure, Brevibloc should be withdrawn. Although withdrawal may be sufficient because of the short elimination half-life of Brevibloc, specific treatment may also be considered. (See Overdosage.)**

Under the PRECAUTIONS section the following subsection was added:

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

Under the PRECAUTIONS/Drug Interactions section the following paragraph was added:

Caution should be exercised when considering the use of _____ and verapamil in patients with depressed myocardial function

Drs. Lipicky and Chen reviewed the labeling and recommended that the wording under the following sections be changed to read as follows:

WARNINGS/Cardiac Failure:

The use of Brevibloc for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with ——— caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium. Despite the rapid onset and offset of ——————— several cases of death have been reported in complex clinical states where Brevibloc was presumably being used ——— to control ventricular rate.

PRECAUTIONS/Drug Interactions:

Caution should be exercised when considering the use of Brevibloc and verapamil in patients with depressed myocardial function. Fatal cardiac arrests have occurred in patients receiving both drugs.

The only difference from the last approved package insert is that this draft did not have labeling for the 1 ~~mg~~ 2mm (10mm strength) strength that was approved in our letter of May 11, 1989 for supplement 7.

Recommendation:

An approvable letter should issue for S-009 pending submission of final printed labeling as set forth under 21 CFR 314.70 (b) (3). [Any change in labeling] In addition to the above changes, the approvable letter should request that the ——————————— paragraph be moved to the Drug Interactions subsection of the PRECAUTIONS section, per Dr. Ganley.

Zelda McDonald

Zelda McDonald, CSO

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