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.

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-386/S-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 At the first sign or symptom of impending cardiac failure, BREVIBLOC should be withdrawn.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.

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