DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

OCT - 1 1999

Priya Jambhekar
Director, Regulatory Affairs
Baxter Pharmaceutical Products Inc.
95 Spring Street
New Providence, NJ 07974

RE: NDA# 19-386
Brevibloc (esmolol hydrochloride) Injection
MACMIS ID# 8298

Dear Ms. Jambhekar:

As part of its routine monitoring program, the Division of Drug Marketing, Advertising and Communications (DDMAC) has become aware of promotional materials for Brevibloc (esmolol hydrochloride) injection, disseminated by Baxter Pharmaceutical Products Inc. (Baxter), that violate the Federal Food, Drug and Cosmetic Act and its implementing regulations. Reference is made to selected promotional materials for Brevibloc, including brochure (13000164) and dosing guide (04-0211/748176), submitted under cover of Form FDA 2253. DDMAC has reviewed these materials and has determined that they are false or misleading, promote unapproved uses, and lack fair balance.

Misleading use of clinical studies to imply clinical benefit/Promotion of unapproved uses

The Indications and Usage section of the approved product labeling (PI) for Brevibloc states that:

> 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 judgment, the rapid heart rate requires specific intervention. Brevibloc is not intended for use in chronic settings where transfer to another agent is anticipated.
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> Brevibloc (esmolol HCl) is indicated for the treatment of tachycardia and hypertension that occur during induction and tracheal intubation, during surgery, on emergence from anesthesia, and in the postoperative period, when in the physician's judgment such specific intervention is considered indicated. Use of Brevibloc to prevent such events is not recommended.

In your brochure, you present numerous claims that imply that Brevibloc is useful for preventing cardiovascular morbidity and mortality.. For example:

- Myocardial ischemia is associated with a nine-fold increase in risk for perioperative cardiac death, myocardial infarction, or unstable angina.
- Beta blockade significantly reduces the number of ischemic events in high-risk patients
- Perioperative beta blockade decreased the number of acute ischemic events by 30%-50%.

These claims are followed by presentation of claims, such as "Brevibloc – the logical choice to control the ischemic cascade," which imply that Brevibloc is useful for reducing morbidity and mortality. However, Brevibloc was not even evaluated in the clinical trial cited as the basis for these claims.[1] Therefore, these claims and representations are misleading because they are not based on substantial evidence derived from adequate and well-controlled clinical trials in which Brevibloc was the drug studied. Furthermore, Brevibloc is not indicated to reduce or prevent cardiovascular morbidity or mortality, thus claims and presentations throughout this brochure that state or imply that Brevibloc is useful in reducing cardiac morbidity or mortality constitute promotion of Brevibloc for unapproved uses.

In addition, you make claims and representations that imply that Brevibloc is useful for preventing atrial fibrillation (AFib) following CABG surgery. For example, you state that "significantly less AFib occurs in patients protected with beta blockers," and present the results of a meta-analysis of 18 randomized studies[2] to support this claim. However, once again, Brevibloc was not evaluated in any of these 18 clinical trials. Furthermore, Brevibloc is not indicated for preventing AFib. Therefore, claims that state or imply that Brevibloc is useful for preventing or reducing the incidence of AFib are misleading because they are not supported by substantial evidence, and promote Brevibloc for an unapproved use.

Finally, you present claims and a table that suggest that Brevibloc is more effective than verapamil or diltiazem in converting acute-onset of AFib or atrial flutter (AFl) to normal sinus rhythm. However, Brevibloc is not indicated for conversion of AFib/AFl to normal sinus rhythm. In fact, the PI for Brevibloc states that use of Brevibloc rarely results in conversion to normal sinus rhythm. Therefore, these claims and representations, including the stated

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1. Wallace A, Layug B, Tateo I, et al. Prophylactic atenolol reduces postoperative myocardial ischemia. *Anesthesiology*. 1998;88:7-17.

2. Andrews TC, Reimold SC, Berlin JA, Antman EM. Prevention of supraventricular arrhythmias after coronary artery bypass surgery: a meta-analysis of randomized control trials. *Circulation*. 1991;84(suppl III):236-244.

superiority over verapamil and diltiazem, are misleading. DDMAC notes that our objections to a similar presentation were previously communicated in a letter, dated December 20, 1991.

Unsubstantiated superiority claims

In the brochure, you present a table that compares various characteristics of selected intravenous agents, including long-acting beta-blockers, calcium channel blockers, digitalis compounds, and opioid analgesics. The table is entitled "Brevibloc provides optimal control." This presentation implies that Brevibloc provides superior efficacy over the other products listed in the table. However, this implication is misleading because it represents an "across-label" comparison that is not supported by head-to-head, adequate and well-controlled clinical trials. Furthermore, many of the intravenous agents compared in this table are not approved for use for the same indications as Brevibloc. DDMAC notes that our objections to a similar "across-label" presentation were previously communicated in a letter, dated December 20, 1991.

Misrepresentation of dosing and administration

In the dosing guide, you present "easy dosing guidelines" as follows:

1. 0.5 mg/kg bolus (500 μg/kg) give over 1 minute.
2. After bolus and initial pump settings are set, dial infusion to desired heart rate.

However, these dosing guidelines are inconsistent with the recommended dosing regimens described in the Dosage and Administration section of the PI for Brevibloc. Therefore, this presentation is misleading because it is inconsistent with the PI and minimizes the importance of the titration process for Brevibloc.

Lacking in fair balance

Promotional materials must present information about the risks associated with the use of the drug with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of the drug. In addition, promotional materials are lacking in fair balance if they contain a representation or suggestion that a drug is safer, has fewer or less incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence. DDMAC has reviewed this brochure and dosing guide and objects to the lack of fair balance with respect to both content and prominence of risk information. Baxter's failure to adequately disclose the risks associated with Brevibloc raises significant patient safety concerns. For example:

Dosing guide

Although you present claims regarding Brevibloc's efficacy on the dosing guide, you have failed to present any information concerning Brevibloc's contraindications, warnings, precautions or adverse reactions (emphasis added). Therefore, this dosing guide fails to disclose the risks associated with Brevibloc therapy, thereby implying that Brevibloc is safer than demonstrated by substantial evidence.

Brochure

In your 12-page brochure, you have presented efficacy claims in large, bolded, bulleted, and colorful type. However, the only risk information disclosed is presented in small sized type, with poor contrast, as a footnoted paragraph, on page 6. Presentation of risk information in this manner is not sufficient to provide prominence and readability reasonably comparable with the presentation of information relating to effectiveness of the drug. Therefore, this promotional brochure is lacking in fair balance.

Furthermore, you have failed to provide adequate content with respect to disclosure of risk information. For example, Brevibloc is contraindicated in patients with sinus bradycardia, heart block greater than first degree, cardiogenic shock or overt heart failure. These contraindications are not presented in the brochure. Also, information from the Warning section of the PI concerning use in patients with cardiac failure, and vasoconstriction associated with hypothermia is not disclosed.

When risk information is presented in this brochure, it is often incomplete and its importance is further minimized by the lack of prominence afforded the presentation. For example, you present claims about the safety of Brevibloc when used in special patients populations, but fail to provide adequate context to qualify these claims. The following examples do not provide an exhaustive list of these violations:

- "Cardioselectivity enhances safety for patients with bronchospastic disease."

  The Warning section of the PI states that "PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS." This risk information is not disclosed. Furthermore, your claim regarding "cardioselectivity" is not qualified to disclose that this preferential effect is not absolute, and that at higher doses it begins to inhibit beta$_2$ receptors located chiefly in the bronchial and vascular musculature.

"Can be used in patients with COPD or diabetes."

Information from the Warning section of the PI concerning the risk of masking signs of hypoglycemia in patients with diabetes is not presented to qualify this claim.

- "Metabolized by red blood cells – does not depend on liver or kidneys for excretion."

  The claim implies that Brevibloc is not associated with risks for patients with impaired renal function. However, the Precautions section of the PI states that "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." This context is not provided to qualify the above claim.

- "Rapidly eliminated, allowing for fast resolution of any adverse effects."

  First, "rapidly eliminated" is not qualified to identify that after termination of the infusion, substantial recovery from beta blockade is observed in 10-20 minutes. Second, this claim implies that adverse events can be universally reversed. However, the Warning section of the PI states that "despite the rapid onset and offset of the effects of Brevibloc, several cases of death have been reported in complex clinical states where Brevibloc was presumably being used to control ventricular rate." The above claim clearly overstates the safety of this product.

Finally, your presentation of information concerning hypotension, the most common adverse event, lacks prominence, is incomplete, and is inconsistent with the PI. First, you have selectively presented only the incidence rates for symptomatic hypotension (12%), and excluded the higher incidence rates for asymptomatic hypotension (25%). Second, you state that "hypotension was readily reversed while on infusion or within 3 minutes of discontinuation in virtually all patients." However, the Adverse Reactions section of the PI states that "asymptomatic hypotension occurred in about 25% of patients. Hypotension resolved during Brevibloc (esmolol HCl) infusion in 63% of these patients and within 30 minutes after discontinuation of infusion in 80% of the remaining patients" (emphasis added). Therefore, your claim is misleading because it is inconsistent with the PI, and implies that the drug is associated with less incidence of side effects than demonstrated by substantial evidence. This misleading presentation could compromise patient safety if physicians expect that hypotension can be "reversed" within 3 minutes.

Baxter should immediately cease distribution of these and other similar promotional materials for Brevibloc that contain the same or similar claims or presentations. Baxter should submit a

written response to DDMAC on or before October 15, 1999, describing its intent and plans to comply with the above. In its letter to DDMAC, Baxter should include a list of the violative promotional pieces that were discontinued, and the date on which such materials were discontinued.

Baxter should direct its response to the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds Baxter that only written communications are considered official.

In all future correspondence regarding this particular matter please refer to MACMIS ID #8298 in addition to the NDA number.

Sincerely,

/S/

Janet Norden, MSN, RN
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications