

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**18-017/S-036**

**Medical Review(s)**



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**Memorandum**

**DATE:** February 25, 2002  
**FROM:** Shari L. Targum, M.D.  
**TO:** #18-017  
**SUBJECT:** Supplement #S-036

Correspondence Date: August 10, 2001  
Sponsor: Merck & Co., Inc.

The sponsor has submitted a labeling supplement for Blocadren® (timolol maleate). This product is currently approved for hypertension, myocardial infarction, and migraine. The usual initial dosage for hypertension and migraine is 10 mg twice daily; the recommended dosage in myocardial infarction is also 10 mg twice daily.

The proposed labeling change involves the following addition of a new Geriatric Use subsection under **Precautions**.

*Geriatric Use (proposed change)*

Clinical studies of BLOCADREN for the treatment of hypertension or migraine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

In a clinical study of BLOCADREN in patients who had survived the acute phase of a myocardial infarction, approximately 350 patients (37%) were 65-75 years of age. Safety and efficacy were not different between these patients and younger patients (see CLINICAL PHARMACOLOGY, *Pharmacodynamics*). Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See PRECAUTIONS, *Impaired Hepatic or Renal Function and Dosing in the Presence of Marked Renal Failure*.)

**Comment:** The above labeling refers to a placebo-controlled timolol study conducted by the Norwegian Multicenter Study Group. According to the Medical Officer Review (MOR) of that trial, 384 placebo patients and 348 patients were 65 years and older (patients over 75 years were excluded and this reviewer was unable to find protocol violations on the basis of age). This

reviewer did not discern age-related (ie, elderly vs. younger) differences in mortality or reinfarction. In fact, the efficacy of timolol appeared to be preserved in the elderly, based on the MOR as well as published literature concerning this trial.

This reviewer conducted a separate literature search of timolol and the elderly. No new or unusual information was found that would alter the proposed labeling.

The sentences referring to renal excretion, taken from CFR 201.57 (10) (iii) (B) are consistent with language already present in the current labeling ("Timolol is partially metabolized by the liver and timolol and its metabolites are excreted by the kidney.")

**Recommendations:**

1. Agree with the proposed Geriatric labeling as drafted by the sponsor.
2. Agree with addition of standard wording from CFR 201.57(10) (iii)(B) since metabolites of this drug is primarily excreted by the kidney.

c.c.: #18-017  
HFD-110  
HFD-110/McDonald  
HFD-110/Stockbridge

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/s/

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Shari Targum  
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MEDICAL OFFICER