**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**18-017/S-036**

# Clinical Pharmacology and Biopharmaceutics Review

**Clinical Pharmacology/Biopharmaceutics Review**

NDA: 18-061/S-029: Timolide® (Timolol Maleate/HCTZ)
Submission Date: August 8, 2002

NDA: 18-017/S-036: Blocadren® (Timolol Maleate)
Submission Date: Augusst 8, 2002

Reviewer: Peter H. Hinderling, MD

**TYPE OF SUBMISSION: Submission of the Geriatrics Use Sections of the Package Inserts for Timolide® and Blocadren®.**

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BACKGROUND:

Timolol Maleate in tablet strengths of 5 mg, 10 mg and 20 mg is indicated for the treatment of hypertension, patients who have survived the acute phase of myocardial infarction and prophylaxis of migraine. The Combination Timolol Maleate-Hydrochlorothiazide in tablet strengths of 5, 10 and 20 mg is indicated for the treatment of hypertension.

The Sponsor submitted language for the Geriatric Use Sections for Timolide® and Blocadren®.

COMMENTS:

The Package Inserts of both products contain Geriatric Use Sections that are not annotated. The Geriatric Use Section for Blocadren® states that there is insufficient data in the elderly available from clinical studies performed by the Sponsor to analyze the impact of age on the efficacy and safety of Blocadren®. It is mentioned that "other clinical evidence reported has not identified differences in responses between the elderly and younger patients". However there is no reference given in support of this statement. An additional statement cautions that the dose selection in the elderly ought to be cautious, because elderly patient could have reduced renal, hepatic or cardiac functions.

The proposed language of the Geriatric Use Section for Timolide® is identical to that for Blocadren® with one exception: Reference is made to a clinical study in survivors of the acute phase of myocardial infarction that showed no difference in efficacy and safety in elderly and younger subjects treated with Timolide®.

Neither Package Insert contains results of PK studies on timolol, hydrochlorothiazide or the combination in the target hypertensive population or in healthy subjects. A literature search on the impact of age on the PK and PD of the active moieties of Blocadren ®and Timolide® covering the period from 1975 to 2002 was performed in-house. Data were collected that were to be from studies investigating the PK and/or PD of timolol or hydrochlorothiazide alone or in combination with other drugs. The data were to be obtained in young and elderly healthy volunteers or hypertensive subjects. The study design and demographics of the investigated subjects were to be defined clearly, the assay was to be specific and sensitive and the data analysis was to be state of the art.

There was no relevant information on the impact of age on the pharmacokinetics of timolol found from the published literature. Five publications described the impact of age on the PK of hydrochlorothiazide in combination with other antihypertensive drugs (1-5). These were open-label, parallel design studies in 6 to12 healthy or hypertensive subjects of different age receiving hydrochlorothiazide in single and/or multiple doses of 12.5 or 25 mg. Hydrochlorothiazide was administered in combination with triamterene, amiloride, atenolol, fosinopril or lisinopril. The references are listed below.

The results of the studies are summarized in Table 1. Drug-drug interactions cannot be excluded. Hence the scenario investigated in the 5 studies was the impact of age on the PK of hydrochlorothiazide in the presence of other diuretics and antihypertensive drugs. This reflects the true clinical situation. There was a consistent increase in the exposure measures Cmax (median: +38%, range: +8-89%) and AUC (median: + 99% (range:+12-171%) in the elderly compared to young and/or middle aged subjects in all 5 studies. Considerable inter-study variation in the AUC values was found. Hypertension per se did not appear to impact the PK of hydrochlorothiazide.

In a multi-center trial the antihypertensive activity of hydrochlorothiazide given alone was not found to be age dependent (6). However, based on the information obtained from three double-blind studies the response to thiazide diuretics including hydrochlorothiazide was found to be greater in older than in younger hypertensive patients (7). Tolerability of thiazide diuretics including hydrochlorothiazide in older hypertensive patients was found to be similar to that in younger patients. Lowering the starting dose of drugs reducing the cardiac output such as thiazide diuretics and beta-blocking agents in elderly hypertensives was recommended. The findings from four studies conducted in general practices with Moducren® (timolol 10 mg, hydrochlorothiazide 25 mg, amiloride 2.5 mg) found no age difference in efficacy or safety of this combination product (8).

RECOMMENDATIONS:

1. The Sponsor should provide annotations (references) supporting the statement on similar efficacy and safety of Blocadren® in elderly and younger hypertensive patients.

2. The cautions expressed by the Sponsor in the proposed Geriatric Use Section for Timolide® and Blocadren® are appropriate.

3. No information on the PK or PD for timolol is available from studies conducted by the Sponsor or from the published literature. Therefore no PK information can be put in the Geriatric Use Section in the Package Insert for Timolide® or Blocadren ® at this time.

4. The observed increase in the exposure measures for hydrochlorothiazide in the elderly ought to be put in the Geriatric Use Section for both Blocadren® and Timolide ®. The following wording is proposed: " The results from 5 single and /or multiple dose PK studies comparing the impact of age on the PK of hydrochlorothiazide, when given in combination with other antihypertensive drugs, were consistent. They indicated a median increase in Cmax and AUC of 38% and 99%, respectively, in elderly relative to younger subjects."

4. The language in the Geriatric Use Section should acknowledge that Timolide® is a drug **combination** and not a single drug (" The drug is known to be substantially excreted by the kidney...." should read "**Both chemical entities contained in** Timolide® are known to be excreted substantially by the kidney.....")

5. The Medical Reviewer ought to review all proposed statements on efficacy and safety in both Package Inserts.

6. The labels of other products containing hydrochlorothiazide ought to be updated accordingly

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RD/FT initialed by Patrick J. Marroum, PhD

cc : NDA 18-071/S-036 HFD 860 (Mehta, Sahajwalla, Hinderling)

**Table 1. Comparative Mean [SD] Parameters of Hydrochlorothiazide in Young and Elderly Subjects**

| Population | | Hydrochlorothiazide Dose, mg | Co-Treatment | Age | n | Cmax, ng/mL | | Tmax,h | | AUC, ng/mLxh | | AUCFactor | | CmaxFactor | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | SD | MD | SD | MD | SD | MD | SD | MD | SD | MD | |
| Young | Healthy | 25 | Triamterene | 41 | 26 | | 455 [185] | | 1.93 [0.76] | | 2714 [871] | | | | | Williams et al 1986 |
| Elderly | Hypert | | | 65 | 13 | | 599 [178] | | 1.80 [1.03] | | 4765 [1653] | | 1.76 | | 1.32 | |
| Young | Healthy | 12.5 | Lisinopril | 46 | 12 | 57.7 | 65.0 | 2 | 2 | 411 | 471 | | | | | Laher et al 1991 |
| | Hypert | | | 72 | 11 | 70.4 | 88.7 | 3 | 2 | 655 | 827 | 1.59 | 1.76 | 1.22 | 1.36 | |
| Young | Healthy | 25 | Triamterene | 25 | 10 | 130 [10] | | 2.0 [0.21] | | 528* | | | | | | Fliser et al 1999 |
| Elderly | Healthy | | | 68 | 11 | 140 [10] | | 2.09 [0.16] | | 595* | | 1.12 | | 1.08 | | |
| Young | Healthy | 25 | Atenolol, Amiloride | 24 | 6 | 297.8 [26.58] | 356.17 [18.26] | | | 3378.50 [349.82] | 3163.33 [260.17] | | | | | Sabanathan et al 1987 |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Elderly | Healthy | | | 74 | 6 | 483.67 [32.19] | 615.0 [43.09] | | | 7633.80 [471.31] | 7648.17 [962.29] | 2.26 | 2.41 | 1.62 | 1.72 | | |
| Elderly | Hypert | | | 71 | 6 | 474.67 [59.87] | 673.17 [87.84] | | | 7000.33 [1267.49] | 8571.50 [1029.7] | 2.07 | 2.71 | 1.59 | 1.89 | | |
| Young | | 12.5 | Fosinopril | 24 | 12 | 60 [18] | 64 [17] | 2 [1.4] | 2 [1.4] | 385 [146] | 401 [132] | | | | | | Much et al 1999 |
| Elderly | | | | 76 | 12 | 77 [16] | 89 [22] | 3 [2.4] | 3 [1.4] | 734 [255] | 765 [174] | 1.91 | 1.91 | 1.28 | 1.39 | | |
| **Median (Range)** | | | | | | | | | | | | **1.99 (1.12-2.71)** | | **1.38 (1.08-1.89)** | | | |

*From AUC=Ae/Clr, where Ae and Clr correspond to the amounts excreted in urine in 24 h following administration and renal clearance, respectively. Repoted AUC values have incorrect units.

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/s/
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