



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: May 28, 2008

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Subject: 1-year Pediatric Exclusivity Postmarketing Adverse Event Review

Drug Name(s): Betaxolol HCl ophthalmic suspension (Betoptic S®)

Pediatric Exclusivity Approval Date: February 28, 2007

Application Type/Number: NDA 19-845

Applicant/sponsor: Alcon

OSE RCM #: 2007-505

## **EXECUTIVE SUMMARY**

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of Betoptic S® (betaxolol HCl ophthalmic suspension) in pediatric patients. Up to the "data lock" date of 3/31/2008, AERS contained 351 reports for Betoptic S® (crude counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately 0.3% of the total (1/351).

DAEA was asked to focus on the 1-year period following the approval of pediatric exclusivity, 2/28/2007 to 2/28/2008. We used an AERS data lock date of 3/31/2008, to allow time for reports received up to 2/28/2008, to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received one report (crude counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent 0% of the total number of cases (0/1). We will refer to this 13-month interval as the pediatric exclusivity period in the remainder of this review.

This review does not reveal any new safety concerns for the use of betaxolol HCl ophthalmic suspension in pediatric patients. We will continue routine monitoring of adverse events with the use of Betoptic S® in pediatric patients.

## **1 BACKGROUND**

### **1.1 INTRODUCTION (PRODUCT FORMULATIONS AND INDICATIONS)**

Betoptic S® (NDA 19-845) is a suspension for ophthalmic use that was approved on 12/29/1989 and is available in a 0.25% strength. It is a cardioselective beta-adrenergic receptor blocking agent that is indicated for the treatment of elevated intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension.

### **1.2 PEDIATRIC FILING HISTORY**

The original Pediatric Written Request (WR) was issued on 10/15/99 and amended on 5/14/2001. The WR was reissued on 3/5/2004. The pediatric efficacy supplement was approved on 6/8/2007 and pediatric exclusivity was granted on 2/28/2007.

### **1.3 PEDIATRIC LABELING**

Under **ADVERSE REACTIONS—Clinical Studies Experience:**

In a 3-month, double-masked, active-controlled, multicenter study in pediatric patients, the adverse reaction profile of BETOPTIC S® Ophthalmic Suspension 0.25% was comparable to that seen in adult patients.

Under the **Pediatric Use** section:

Safety and IOP-lowering effect of BETOPTIC S® Ophthalmic Suspension 0.25% has been demonstrated in pediatric patients in a 3-month, multicenter, double-masked, active-controlled trial.

## 2 METHODS AND MATERIALS

### 2.1 INTRODUCTION

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

### 2.2 AERS SELECTION OF CASES

AERS was searched on 5/20/2008 using the trade name Betoptic S and the advanced criteria NDA 019845 for all events with an FDA received date from 12/29/1989 through 3/31/2008, and for all events with an FDA received date from 2/28/2007 through 3/31/2008. The above searches were repeated for domestic cases only.

## 3 AERS RESULTS FOR BETOPTIC S

### 3.1 COUNT OF REPORTS: ALL SOURCES- US AND FOREIGN FROM MARKETING APPROVAL (TABLE 1)

<b>Table 1: Crude counts<sup>1</sup> of AERS Reports for All Sources from Marketing Approval Date</b>			
<b>(US counts in parentheses)</b>			
	All reports (US)	Serious <sup>2</sup> (US)	Death (US)
Adults (≥ 17 yrs.)	181 (180)	9 (8)	2 (1)
Pediatrics (0-16 yrs.)	1 (1)	0 (0)	0 (0)
Age unknown (Null values)	169 (168)	5 (4)	1 (0)
Total	351 (349)	14 (12)	3 (1)

<sup>1</sup> May include duplicates

<sup>2</sup> Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, and congenital anomaly.

### 3.2 COUNT OF REPORTS: ALL SOURCES- US AND FOREIGN FROM PEDIATRIC EXCLUSIVITY (TABLE 2)

Table 2: Crude counts <sup>1</sup> of AERS Reports for All Sources from date Pediatric Exclusivity was Granted (US counts in parentheses)			
	All reports (US)	Serious <sup>2</sup> (US)	Death (US)
Adults (≥ 17 yrs.)	1 (0)	1 (0)	1 (0)
Pediatrics (0-16 yrs)	0 (0)	0 (0)	0 (0)
Age unknown (Null Values)	0 (0)	0 (0)	0 (0)
Total	1 (0)	1 (0)	1 (0)
<sup>1</sup> May include duplicates			
<sup>2</sup> Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, and congenital anomaly.			

## 4 DISCUSSION/SUMMARY OF CASES

There were no pediatric cases received during the 1-year post-pediatric exclusivity period.

The one case that was received during the exclusivity period involved an 85-year-old female in the United Kingdom who had reported adverse events of presyncope, wheezing, arrhythmia, atrial fibrillation, and death unexplained. Wheezing was associated with timolol maleate 0.25% eye drops, which necessitated a switch to Betoptic S. The presyncopal symptoms started after the substitution. Her symptoms were felt to be due to poorly controlled atrial fibrillation with suboptimal rate control leading to presyncope. A regular oral beta blocker was associated with complete resolution of all her symptoms. The patient died in [REDACTED], but no mention was made if it was related to any of the adverse events. The events occurred in 2004, but the term "arrhythmia" was listed four times with dates beginning as early as January 2004.

The one pediatric case in the database involved a 3-year-old male who was treated with Betoptic S for glaucoma. One month after starting therapy, the mother reported her son became noticeably more hyperactive and struggled with his speech. The child has a history of delayed development. The patient was switched to Timoptic. However, it was determined that the events were unrelated to Betoptic S, but associated with an OTC cough and cold preparation.

## 5 CONCLUSION

This review does not reveal any new safety concerns for the use of betaxolol HCl ophthalmic suspension in pediatric patients.

## 6 RECOMMENDATIONS

We will continue routine monitoring of adverse events with the use of Betoptic S® in pediatric patients.

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/s/

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