



**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

To: Lisa L. Mathis MD, Associate Director
Pediatric and Maternal Health Staff (PMHS)
Office of New Drugs (OND), CDER
and
M. Dianne Murphy, MD, Director
Office of Pediatric Therapeutics (OPT), OC

From: Ronald Wassel, Pharm.D., Safety Evaluator
Division of Adverse Event Analysis II

Through: Melissa Truffa, R.Ph., Team Leader
Division of Adverse Event Analysis II
Ann McMahon, MD, MS, Acting Director
Division of Adverse Event Analysis II
Office of Surveillance and Epidemiology (OSE), CDER

Subject: 1-year Pediatric Exclusivity Postmarketing Adverse Event Review

Drug Name(s): Timolol maleate ophthalmic gel forming solution (Timolol GFS)

Pediatric Exclusivity Approval Date: February 28, 2007

Application Type/Number: NDA 20-963

Applicant/sponsor: Falcon

OSE RCM #: 2007-506

EXECUTIVE SUMMARY

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of Timolol GFS (timolol maleate ophthalmic gel forming solution) in pediatric patients. Up to the "data lock" date of 3/31/2008, AERS contained 30 reports for Timolol GFS (crude counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately 3.3% of the total (1/30).

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 timolol maleate ophthalmic gel forming solution in pediatric patients. We will continue routine monitoring of adverse events with the use of Timolol GFS in pediatric patients.

1 BACKGROUND

1.1 INTRODUCTION (PRODUCT FORMULATIONS AND INDICATIONS)

Timolol GFS (NDA 20-963) is a gel forming solution for ophthalmic use that was approved on 10/21/1998 and is available in 0.25% and 0.5% strengths. It is a beta-adrenergic receptor inhibitor that is indicated for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

1.2 PEDIATRIC FILING HISTORY

The original Pediatric Written Request (WR) was issued on 10/15/99 and amended two times, on 5/14/2001, and 3/12/2004. The pediatric efficacy supplement was approved on 6/8/2007 and pediatric exclusivity was granted on 2/28/2007.

1.3 PEDIATRIC LABELING

Under the **Pediatric Use** section:

Safety and IOP-lowering effect of Timolol GFS 0.25% and 0.5% 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 existing product group for timolol (Owner—Ronald Wassel) and the advanced criteria NDA 020963 for all events with an FDA received date from 10/21/1998 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 TIMOLOL GFS

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

Table 1: Crude counts¹ of AERS Reports for All Sources from Marketing Approval Date			
(US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	14 (13)	9 (8)	0 (0)
Pediatrics (0-16 yrs.)	1 (1)	1 (1)	0 (0)
Age unknown (Null values)	15 (14)	3 (2)	0 (0)
Total	30 (28)	13 (11)	0 (0)
¹ May include duplicates			
² 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 counts¹ of AERS Reports for All Sources from date Pediatric Exclusivity was Granted			
(US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	0 (0)	0 (0)	0 (0)
Pediatrics (0-16 yrs)	0 (0)	0 (0)	0 (0)
Age unknown (Null Values)	1 (0)	1 (0)	0 (0)
Total	1 (0)	1 (0)	0 (0)
¹ May include duplicates			
² 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.

There was one case reported during the 1-year post-pediatric exclusivity period in a female patient of unknown age from Italy who experienced severe pain and severe ocular disease soon after timolol maleate 0.5% eye drops administration. On February 3, 2007 she was referred to the Emergency Unit Room where she was diagnosed with a corneal abrasion and diffuse dysepithelization. The patient was prescribed bandaging for 36 hours and 7 days instillation of levofloxacin and hyaluronic acid 0.15% eye drops.

Timolol maleate ophthalmic solution is included in combination products with brimonidine tartrate (Combigan™) and dorzolamide HCl (Cosopt®). A search of AERS with these combination products found 43 reports for Combigan™ (0 pediatric reports) and 436 reports for Cosopt® (3 pediatric reports). The three pediatric reports for Cosopt® are described briefly:

AERS CASE # 3374426 (US)—A 7-month-old male was placed on therapy with Cosopt® in both eyes for the treatment of congenital glaucoma (duration unknown). Concomitant therapy included unspecified "ocular medications." After the patient had taken Cosopt® for 3-4 months, the patient's mother called to report that the patient's right eye looked "cloudy." On examination the patient was found to have "developed severe corneal edema in the right eye." The ophthalmologist stated that the patient's mother had been administering the eye drops three times a day instead of twice daily as prescribed. Subsequently, therapy with Cosopt® was discontinued (as well as all of the patient's other ocular medications) and the patient recovered from the events.

AERS CASE # 5720629 (FRANCE)—A 4-year-old male with bilateral congenital glaucoma treated with Cosopt® and travaprost was hospitalized with arterial hypertension and paroxysmic abdominal pain. Nicardipine was administered orally, then IV, then orally again (15 mg x 3). There was subsequent progressive decrease of abdominal pain and normalization of arterial tension (treatment for 6 months). Both ophthalmic products had been continued.

AERS CASE # 6167884 (FRANCE)—A 36-year-old female patient with type I diabetes mellitus, diabetic nephropathy and osteitis was placed on therapy with Cosopt® for glaucoma. Concomitant therapy included clindamycin, ramipril, ofloxacin, insulin, injection, and latanoprost. The patient became pregnant and ultrasound revealed intra-uterine death at 7 weeks gestation. Action taken regarding all therapies was unknown.

5 CONCLUSION

This review does not reveal any new safety concerns for the use of timolol maleate ophthalmic gel forming solution in pediatric patients.

6 RECOMMENDATIONS

We will continue routine monitoring of adverse events with the use of Timolol GFS in pediatric patients.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ronald Wassel
5/28/2008 08:53:47 AM
DRUG SAFETY OFFICE REVIEWER

Melissa Truffa
5/28/2008 08:56:45 AM
DRUG SAFETY OFFICE REVIEWER

Ann W McMahon
5/31/2008 04:41:43 PM
DRUG SAFETY OFFICE REVIEWER