

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

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SUBJECT: One Year Post-Pediatric Exclusivity Post marketing Adverse Event Review: Drug Use Data
Trusopt® Dorzolamide Hydrochloride (NDA 20-408)
Pediatric Exclusivity Approval Date: January 5, 2004

****This document contains proprietary data from IMS Health and Caremark which cannot be shared outside of the FDA without clearance from IMS Health and Caremark through the Office of Drug Safety.****

EXECUTIVE SUMMARY

This consult examines drug use trends for Trusopt® (dorzolamide hydrochloride) in the pediatric population (0-16 years), with primary focus on patterns of use one year before and one year following the granting of Pediatric Exclusivity on January 5, 2004.

Total dispensed prescriptions for the single ingredient product Trusopt® (dorzolamide HCl) decreased approximately 7% from approximately 872,000 dispensed prescriptions from February 2003 to January 2004, inclusive, to approximately 807,000 dispensed prescriptions from February

2004 to January 2005, inclusive. During the same two 12-month time periods, total dispensed prescriptions for the combination product, Cosopt[®] (dorzolamide HCl/timolol maleate), increased approximately 8% from approximately 2.6 million prescriptions dispensed from February 2003 to January 2004, inclusive, to slightly over 2.8 million dispensed prescriptions from February 2004 to January 2005, inclusive.

Among an insured population in the Caremark system, the pediatric age group (1-16 years) accounted for roughly 0.5% of claims paid for both Trusopt[®] and Cosopt[®] between February 1, 2004 and January 31, 2005. Because the number of pediatric claims were so small, we did not attempt to use them to estimate the volume of prescriptions dispensed nationwide.

Projected numbers of diagnosis mentions in IMS Health's National Disease and Therapeutic Index[™] for Trusopt[®] and Cosopt[®] in the pediatric age group (0-16 years) during the study period were too small to include in this analysis.

Pediatricians were responsible for roughly 0.3 % (approximately 2,000 prescriptions) of all Trusopt[®] and 0.3% (approximately 7,000 prescriptions) of all Cosopt[®] prescriptions dispensed in the U.S. from February 2004 through January 2005.

INTRODUCTION

On January 3, 2001, Congress enacted the Best Pharmaceuticals for Children Act (BPCA) to improve the safety and efficacy of pharmaceuticals for children. Section 17 of the BPCA requires the reporting of adverse events associated with the use of the drug in children during the one-year period following the date when the drug received marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee on the drug utilization patterns and adverse events associated with the use of the drug on a quarterly basis. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs through the MedWatch program.

Dorzolamide HCl (Trusopt[®]) is a carbonic anhydrase inhibitor formulated for topical ophthalmic use. Trusopt[®] is a sterile ophthalmic 2% solution of dorzolamide hydrochloride available in 5 ml and 10 ml OCUMETER PLUS[®] containers. Trusopt[®] was approved under (NDA 20-408) on December 9, 1994. Dorzolamide HCl is also available as an ophthalmic formulation in combination with the beta adrenergic receptor blocking agent, timolol maleate, under the brand name Cosopt[®] which was approved on April 7, 1998 under (NDA 20-869). Cosopt[®] and Trusopt[®] are both manufactured by Merck and Co. © and are both indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma by reducing aqueous humor secretion. The safety and efficacy of Trusopt[®] have been demonstrated in pediatric patients in a 3-month, multicenter, double-masked, active-treatment-controlled trial. The dose is one drop of Trusopt[®] to the affected eye(s) three times daily. The dose for Cosopt[®] is

one drop to affected eye(s) twice daily. The safety and efficacy of Cosopt[®] in pediatric patients has not been established.

The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for Trusopt[®] on January 5, 2004.

We will use the term Trusopt[®] to refer to the ophthalmic form of dorzolamide HCl, and Cosopt[®] to refer to the combination formulation of dorzolamide HCl and timolol maleate, unless otherwise specified. To date, there are no generic competitors for either product. The only other product in the topical ophthalmic carbonic anhydrase inhibitor market is brinzolamide (Azopt[®]), which was approved on April 1, 1998.

This review describes outpatient drug usage of Trusopt[®] and Cosopt[®] in the pediatric population as compared to the adult population. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

DATA SOURCES

Sales data reflecting the number of bottles sold by the manufacturer to various retail and non-retail channels of distribution were analyzed using IMS Health's, National Sales Perspectives[™] database. Because greater than 75% of sales of this product occurred in the outpatient setting from February 2004 through January 2005, we only examined the outpatient drug utilization of these products (Table 1). Outpatient Trusopt[®] dispensed prescriptions were measured by IMS Health's National Prescription Audit *Plus*[™] (NPA *Plus*[™]), along with prescription claims for a 36-month period of time from Caremark (Dimension Rx).

I. OUTPATIENT DRUG USE

IMS HEALTH, NATIONAL PRESCRIPTION AUDIT PLUS[™] (NPA PLUS[™])

NPA Plus[™] measures the retail dispensing of prescriptions, or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. These retail pharmacies include chain, independent, food store, mail order, discount houses, and mass merchandiser pharmacies, as well as nursing home (long-term care) pharmacy providers. Information on the specialty of the prescribing physician can also be collected, except for long-term care and mail order pharmacy settings.

The number of dispensed prescriptions is obtained from a sample of approximately 22,000 pharmacies throughout the U.S. and projected nationally. The pharmacies in the database account for approximately 40% of all pharmacy stores and represent approximately 45% of prescription coverage in the U.S.

Data for this analysis included all prescriptions dispensed from February 1, 2002 through January 31, 2005, inclusive.

IMS HEALTH, NATIONAL SALES PERSPECTIVES™

IMS Health National Sales Perspectives™ measures the volume of drug products (both prescription and over-the-counter) and selected diagnostic products moving from manufacturers into retail and non-retail markets. The volume of drug products transferred to these markets is expressed in terms of sales dollars, vials, and market share. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. These data are based on national projections.

For this analysis, sales for Trusopt® and Cosopt® was examined from February 1, 2000 – January 31, 2005 inclusive (the most current data available at the time of this analysis).

CAREMARK DIMENSION RX

Caremark is one of the largest pharmacy benefit manager (PBM) companies in the US, currently covering over 75 million participant lives, and processing over 450 million prescription claims annually. Participants whose claims are processed by Caremark are covered under various types of insurance plans, including health maintenance organizations (HMOs), employers' self-insured health plans, selected managed care plans, and other selected traditional health insurers. Caremark includes participants from all 50 states and includes special populations such as the elderly, children, and women of childbearing age. The representativeness of those included in the Caremark system to all persons receiving dispensed prescriptions in the U.S. is not known however.

For this analysis, prescription claims in the Caremark system were examined from February 1, 2002 through January 31, 2005, inclusive.

RESULTS

I. Sales and Distribution Channels

National Trusopt® sales were examined for the 12 month period from February 2004 through January 2005 in terms of bottles sold (Table 1). During this time period, approximately 1,242,600 bottles of Trusopt® were sold in the U.S., with retail sales accounting for 76% of

volume (Table 1). Mail order accounted for almost 20% of retail sales (data not shown). During this same time period, approximately 3.8 million bottles of Cosopt® were sold in the U.S., with retail sales accounting for 84% of these sales (Table 1).

Table 1: Sales of Bottles (Eaches) of Trusopt® and Cosopt® Sold Through Retail and Non-Retail Channels of Distribution During February 2004 – January 2005 in IMS Health, National Sales Perspectives™

		February 2004 – January 2005	
		Bottles (000's)	(%)
Trusopt®	Total	1242.6	(100)
	*Retail	938.5	(75.5)
	**Non-Retail	304	(24.5)
Cosopt®	Total	3775.1	(100)
	*Retail	3174.5	(84.1)
	**Non-Retail	600.5	(15.9)

*Retail Sales Channels include Chain Stores, Food Stores, Independent, and Mail Service

**Non-Retail channels include non-federal hospitals, federal facilities, clinics, long term care, HMO's, home health care, misc-prison, misc-universities, misc-other.

IMS Health, IMS National Sales Perspectives™, Moving Annual Totals: February 2002 – January 2005, Data

Extracted April 2005

Original File: 0504tru2.dvr

I. Dispensed Prescriptions

Dispensed prescriptions for the single ingredient product, Trusopt®, decreased approximately 7% from approximately 872,000 dispensed prescriptions from February 2003 through January 2004, inclusive, to approximately 807,000 prescriptions dispensed from February 2004 to January 2005, inclusive (Table 2). Dispensed prescriptions for the combination product Cosopt® increased roughly 8% from approximately 2.6 million prescriptions dispensed from February 2003 to January 2004 to slightly over 2.8 million prescriptions dispensed from February 2004 to January 2005. (Table 2).

Table 2: Total Number of Prescriptions Dispensed in Retail Pharmacies Nationwide for Topical Ophthalmic Carbonic Anhydrase Inhibitors (USC5-61650) and Cosopt®

	Feb 2002-Jan 2003		Moving Annual Totals Feb 2003-Jan 2004		Feb 2004-Jan 2005	
	N	(%)	N	(%)	N	(%)
	3,911,000	(100)	3,978,000	(100)	4,169,000	(100)
Dorzolamide (Trusopt®)	975,000	(24.9)	872,000	(22)	807,000	(19.3)
*Dorzolamide/Timolol Maleate (Cosopt®)	2,434,000	(62.2)	2,600,000	(65.3)	2,809,000	(67.4)
Brinzolamide (Azopt®)	502,000	(12.9)	506,000	(12.7)	553,000	(13.3)

* Cosopt® classified by IMS Health as USC5-61690 (miotics and glaucoma, other)

IMS Health, National Prescription Audit Plus™, Moving Annual Totals: February 2002-January 2005, Extracted March 2005.

Original file: 0503tru1.dvr.

The top prescriber specialty for Trusopt® from February 2004 through January 2005 was ophthalmology (approximately 72.5%). Pediatricians accounted for only 0.3% (approximately 2,000 prescriptions) of the dispensed Trusopt® prescriptions (Table 3). The top prescriber specialty for Cosopt® from February 2004 through January 2005 was ophthalmology (approximately 79.4%), with pediatricians accounting for only 0.3% of the dispensed prescriptions (Table 3). There appears to have been no meaningful changes in prescriber specialty for Trusopt® or Cosopt® during the 36-month study period from February 2002 through January 2005.

Table 3: Total Number of Prescriptions Dispensed by MD Specialty in the U.S. Retail Setting for Trusopt® and Cosopt® (excludes Long Term Care and Mail Order Channels*)

Dorzolamide HCl		Moving Annual Totals					
		Feb 2002-Jan 2003		Feb 2003-Jan 2004		Feb 2004-Jan 2005	
Plain Formulation		N	(%)	N	(%)	N	(%)
TRUSOPT®		787,000	(100)	705,000	(100)	651,000	(100)
1 st	Ophthalmology	578,000	(73.5)	518,000	(73.5)	472,000	(72.5)
2 nd	Unknown	69,000	(8.8)	62,000	(8.81)	49,000	(7.6)
3 rd	Optometry	29,000	(3.7)	28,000	(3.9)	29,000	(4.5)
4 th	Veterinary Medicine	10,000	(1.3)	11,000	(1.6)	19,000	(2.9)
5 th	Internal Medicine	22,000	(2.8)	20,000	(2.8)	19,000	(2.9)
11 th	Pediatrics	3,000	(0.3)	2,000	(0.4)	2,000	(0.3)
16 th	Total Others	76,000	(9.6)	64,000	(9)	61,000	(9.3)
Combination Formulation							
COSOPT®		2,080,000	(100)	2,221,000	(100)	2,378,000	(100)
1 st	Ophthalmology	1,643,000	(79)	1,761,000	(79.3)	1,889,000	(79.4)
2 nd	Unknown	155,000	(7.4)	158,000	(7.1)	151,000	(6.3)
3 rd	Optometry	71,000	(3.4)	82,000	(3.7)	100,000	(4.2)
4 th	Osteopathic Medicine	47,000	(2.3)	50,000	(2.2)	52,000	(2.2)
5 th	Internal Medicine	40,000	(1.9)	45,000	(2)	51,000	(2.2)
11 th	Pediatrics	7,000	(0.3)	7,000	(0.3)	7,000	(0.3)
16 th	Total Others	117,000	(5.7)	118,000	(5.4)	128,000	(5.4)

IIMS Health, National Prescription Audit Plus™, Moving Annual Totals: February 2002-January 2005, Data Extracted March 2005
Original file: 0503tru5.dvr.

II. Patient Demographics

Among an insured population managed by Caremark, approximately 0.5% of processed claims for both Trusopt® and Cosopt® were for persons aged 1-16 years for the two 12-month time periods, February 2003 through January 2005 (Table 4).

Total Trusopt® claims decreased approximately 6%, from 98,254 claims in the time period of February 2003 through January 2004 to 92,688 claims (February 2004 through January 2005). Pediatric claims for Trusopt® remained stable between the two 12-month time periods (473 and 472 claims, respectively). Total Cosopt® claims increased roughly 9% from 327,964 claims in February 2003 through January 2004 to 355,970 claims in February 2004 through January 2005. Pediatric paid claims for Cosopt® increased approximately 8%, from 1,648 to 1,775 paid claims, between these time periods.

**Table 4: Total Number of Claims for Trusopt® and Cosopt®
From Caremark Pharmacy Benefit Manager Claims Database.**

	Feb 2002-Jan 2003		Moving Annual Totals Feb 2003-Jan 2004		Feb 2004-Jan 2005	
	N	(%)	N	(%)	N	(%)
TOTAL	413,382	(100)	426,218	(100)	448,658	(100)
TRUSOPT®	110,166	(26.6)	98,254	(23.1)	92,688	(20.7)
Peds (1-16 yrs)	500	(0.5)	473	(0.5)	472	(0.5)
Adults (17+ yrs)	109,666	(99.5)	97,781	(99.5)	92,216	(99.5)
COSOPT®	303,216	(73.4)	327,964	(76.9)	355,970	(79.3)
Peds (1-16 yrs)	1,361	(0.4)	1,648	(0.5)	1,775	(0.5)
Adults (17+ yrs)	301,855	(99.6)	326,316	(99.5)	354,195	(99.5)

Caremark Dimension Rx™: Extracted March 21, 2005

LIMITATIONS

NPA Plus™ data provide an estimate of the total number of prescriptions dispensed in the U.S. However, NPA Plus™ does not include demographic information, such as age and gender. The inclusion of prescriber specialty data in this report does not include mail order and long-term care channels. This may be significant as mail order (~ 19%) and long-term care (~9%) contributed to total sales of Cosopt® and Trusopt® in the U.S. (Data not shown).

Caremark data cannot be projected to make national level estimates of use, but it can be used to gain insights on the relative use of these products among pediatric participants with claims processed by Caremark. Although the data from the Caremark system may not be nationally representative, they provide a useful description of prescription drug use in the U.S. for a large proportion of the population with prescription drug coverage.

CONCLUSION

Total dispensed prescriptions for the single ingredient product Trusopt® (dorzolamide HCl) decreased approximately 7% from approximately 872,000 dispensed prescriptions from February 2003 to January 2004, inclusive, to approximately 807,000 dispensed prescriptions from February 2004 to January 2005, inclusive. During the same two 12-month time periods, total dispensed prescriptions for the combination product, Cosopt® (dorzolamide HCl/timolol maleate), increased approximately 8% from approximately 2.6 million prescriptions dispensed from February 2003 to January 2004, inclusive, to slightly over 2.8 million dispensed prescriptions from February 2004 to January 2005, inclusive.

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