

# Public Assessment Report

## Paediatric data

### **COSOPT eye drops solution**

Dorzolamide Hydrochloride

Timolol Maleate

**Marketing Authorisation Holder: Merck Sharp & Dohme**

<b>Rapporteur:</b>	Denmark
<b>Co-Rapporteur:</b>	France
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## I. INTRODUCTION

As a part of the EU work sharing project in the assessment of paediatric data, the MAH has submitted available data in children for Cosopt. The available data pertain from the open label phase following a masked double-blind controlled study with Trusopt, as described below. A total of 30 patients in the age  $\geq 2$  but  $< 6$  years were exposed to Cosopt.

Based on the review, the paediatric data should lead to an amendment of the currently approved SPC text. The finally agreed changes to the SPC are shown in section IV at the end of this assessment report.

### I.1 Scope of the assessment

The present variation has been submitted under the EU work sharing project assessment of paediatric data. Currently, an application for TRUSOPT® (dorzolamide 2 % eye drops) is under assessment and a public Assessment Report by the Paediatric Medicines Working Group of Committee on Safety of Medicines, including a recommendation for changes in the SPC, is available (MHRA website: [www.mhra.gov.uk](http://www.mhra.gov.uk)). Reference is made to the report in this assessment.

Cosopt has currently the therapeutic indication and posology:

*COSOPT is indicated in the treatment of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or pseudoexfoliative glaucoma when topical beta-blocker monotherapy is not sufficient.*

*The dose is one drop of COSOPT in the [conjunctival sac of the] affected eye(s) two times daily.*

TRUSOPT has been approved via the MRP in 1995 with France as RMS. Renewal for the product was approved in February 2005. COSOPT has been approved via the MRP in 1998 with Denmark as the RMS.

It should be noted that no separate studies with Cosopt have been conducted. The available data pertain from the open label phase following a masked double-blind controlled study with Trusopt, as described below. A total of 30 patients in the age  $\geq 2$  but  $< 6$  years were exposed to Cosopt.

For clarity, the assessment below includes the assessment of Trusopt.

#### **Background to congenital and juvenile glaucoma**

Glaucoma in childhood is a diverse, blinding group of conditions which has one common feature: raised intra-ocular pressure (IOP). The classification is broadly grouped into congenital (primary developmental anomalies present in the drainage angle or secondary to other ocular or other developmental anomalies) and juvenile onset. Treatment is primarily surgical with medical treatments used as an adjunct. Beta-adrenoceptor blockers have remained first line topical therapy when no contraindications, such as asthma, exist. Clinical opinion is that topical carbonic anhydrase inhibitors appear to be less effective than beta-blockers, but safe systemically, although associated with local irritation and are considered useful as an adjunct to beta-blockers or as first line therapy when beta-blockers are contraindicated. Prostaglandins are not considered as effective in childhood glaucoma as in adult glaucoma, but may have a role in some patients with juvenile open angle glaucoma and others with aphakic glaucoma. Alpha-adrenergic agonists, although effective at least in the short-term, are considered to have serious, potential systemic side effects, which demand close observation when used in neonates and young infants.

***This section summarises important information on COSOPT in the SPC***

COSOPT is comprised of two components: dorzolamide hydrochloride and timolol maleate. Each of these two components decreases elevated intraocular pressure by reducing aqueous humor secretion, but does so by a different mechanism of action.

Dorzolamide hydrochloride is a potent inhibitor of human carbonic anhydrase II. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. Timolol maleate is a nonselective beta-adrenergic receptor blocking agent. The precise mechanism of action of timolol maleate in lowering intraocular pressure is not clearly established at this time, although a fluorescein study and tonography studies indicate that the predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed. The combined effect of these two agents results in additional intraocular pressure reduction compared to either component administered alone.

Following topical administration, COSOPT reduces elevated intraocular pressure, whether or not associated with glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. COSOPT reduces intraocular pressure without the common side effects of miotics such as night blindness, accommodative spasm and pupillary constriction.

## **II. SCIENTIFIC DISCUSSION**

### **II.1 Quality aspects**

Not applicable.

### **II.2 Non-clinical aspects**

Not applicable.

### **II.3 Clinical aspects**

#### **II.3.1 Clinical pharmacology**

No such studies were conducted.

***Rapporteur's comment:***

*The dosing regimen was chosen according to FDA request. The dorzolamide 2 % twice daily regimen in monotherapy is consistent with the approved EU SPC. However, in adjunctive therapy the approved dosage is b.i.d. daily, i.e. lower than the t.i.d regimen used in this study.*

#### **II.3.2 Clinical efficacy**

The MAH has submitted one study with the purpose to document the safety profile of dorzolamide 2.0 % t.i.d. in the paediatric population below 6 years of age.

#### **Methods**

The study was a randomised, 3-months double-masked, active-controlled, multi-centre study to investigate the safety and ocular hypotensive effect of dorzolamide 2 % t.i.d. in paediatric patients with glaucoma, younger than 6 years. Timolol maleate gel-forming solution (timolol GS) once daily (q.d.) was the active treatment control (for patients < 2 years the strength was 0.25 % and for patients ≥ 2 years, but < 6 years

the strength was 0.5 %). Patients were randomised 2:1 with respect to dorzolamide: timolol GS therapy. If IOP was inadequately controlled on monotherapy, a change was made to open-label concomitant therapy of dorzolamide 2 % t.i.d. and timolol GS 0.25 % q.d for patients < 2 years, or combination therapy of dorzolamide 2 % / timolol 0.5 % (COSOPT®) b.i.d., for patients ≥ 2 but <6 years. Inclusion criteria encompassed IOP ≥ 22 mm Hg in suspected or confirmed glaucoma patients. Patient with recent glaucoma surgery, trauma, ocular infection or inflammation, renal dysfunction were excluded. One eye in each patient was included in the study. Current topical or systemic ocular hypotensive medication was discontinued at a pre-study evaluation visit and the duration of any wash-out period was left to the Investigator's discretion. However, (appropriate) guidance for wash-out periods of standard IOP decreasing specified anti-glaucoma medication was provided. Visits were scheduled at weeks 1, 4, and 12, and 2 weeks after stopping the study medication. At the visits it was to be decided if the patients should continue with masked monotherapy, or if they should switch to open-label concomitant/combination therapy.

**Rapporteur's comment:**

*The MAH has appropriately considered published information about plasma levels in paediatric glaucoma patients exceeding oral therapeutic timolol levels in a study measuring plasma levels following topical ocular application. Furthermore, apnoea has been reported in timolol-treated infants. Therefore, the 0.25 % concentration was chosen for children < 2 years and 0.5 % for children ≥ 2 but <6 years. Although based on scarce information this is not to be criticised. The choice of timolol as comparator is appropriate as this drug has the approved paediatric therapeutic indication, albeit not in newborn and premature infants. The recommended dosing is 0.25 % or 0.5 % twice daily. However, the gel formulation is not recommended for use in children. The MAH should justify the choice of using the gel formulation.*

**Co-rapporteur's comment:**

*This is a complete description of the study carried out for Trusopt 2% for a better understanding; however, Cosopt was only used in the open label phase for children of the older cohort of age (i.e. ≥2 years and < 6 years).*

*Therapy was changed on the basis of clinical judgment as to when IOP was uncontrolled. No indication of the IOP levels at which this was made has been provided. It is likely that different clinicians will have different thresholds for this change.*

*Given the seriousness of the disease state under study, it would have been unethical to use a placebo comparator. Instead, timolol gel-forming solution was the active comparator in this study, in accordance with the FDA Written Request. Moreover, ophthalmologists consider this well known beta-blocking agent as a usual reference product for treatment of pediatric glaucoma even if to date it was not registered as such (Denis Ph, J. Fr. Ophthalmol., 2005; 28 Hors série2, 2S35-40).*

The choice of dose for the comparator was changed on the basis of a published study of topical administrations of timolol in adult and pediatric glaucoma patients. The study showed that plasma levels of timolol measured in 3 children below the age of 2 years (3 weeks, 4 months, and 14 months) exceeded oral therapeutic levels; few cases of apnea were also reported in timolol-treated infants. Finally, as the current clinical practice preferably initiated children treatment with timolol 0.25%, this strength was selected for patients <2 years of age and the 0.5% one for patients from 2 years to <6 years of age.

**Objectives:** The study objectives in the submitted trial (MK-0507) were to document an acceptable safety profile for initial therapy with dorzolamide 2 % t.i.d applied for up to 3 months in a population of paediatric patients, divided in 2 age strata; patients <2 years and ≥2 years but <6 years, with elevated IOP or glaucoma.

**Outcomes/endpoints:** The primary hypothesis was that the true proportion of patients who would discontinue because of drug-related adverse events would be ≤25 %. The primary safety measure was the proportion of patients who discontinued because of a drug-related adverse event. The secondary objectives

were to characterise the IOP-lowering effect of dorzolamide 2 % t.i.d and the need for additional therapy, and to characterise the effect of dorzolamide 2 % t.i.d on total CO<sub>2</sub>.

Sample size was determined based on whether a proportion of < 25 % of patients in each age group discontinued because of a drug related adverse event, based on the upper limit of 95 % CIs. The target of patients was 50 in each age cohort.

***Rapporteur's comment:***

*A proportion of ≤ 25 % withdrawing because of adverse events is not ambitious, and rare events are likely not to be caught.*

***Co-rapporteur's comment:***

*No justification is available regarding the choice of this wide limit of discontinuation. It appears artificial and highly motivated by the understandable Applicant's objective of reaching positive results from a study that includes a limited number of pediatric patients.*

*Moreover, the Applicant's reference to previous studies in adult patients treated with dorzolamide for a similar period is not convincing, as the rate of discontinuations due to drug-related adverse experiences reached only 2.7% in these cases.*

Total CO<sub>2</sub> was determined at Day 1 and week 12.

Statistical methods. All- Patients-Treated (APT) was to be the primary set, but a PP analysis was to be conducted as well.

No major changes in conduct of study or analyses were issued.

The study was conducted at 22 USA and 13 non-USA sites.

## **RESULTS**

### **Efficacy evaluation**

Please note that the efficacy analyses IOP change from baseline are based on the 12 weeks IOP assessment regardless of if the patients stayed on monotherapy or were switched to concomitant/combo treatment.

***Co-rapporteur's comment:***

*It should be noted that the IOP-lowering effect of dorzolamide 2% was only a secondary objective of this pediatric study when safety was the primary one.*

*It should be reminded that only the pediatric patients of the older age cohort who switched to the open label combination phase were under Cosopt, representing 30 pediatric patients of ≥ 2 years but <6 years of age.*

*The main analysis was done on the sample of randomized patients who received at least one treatment dose as allocated by the randomization.*

### Age group < 2 years

A number of 83 patients were randomised 56 and 27 in the dorzolamide and timolol groups, respectively. A number of 66 patients completed the trial: 44 (53 %) in the masked monotherapy phase and 22 (27 %) in the open label concomitant/combination phase. The proportion who discontinued from the two treatment groups were similar, namely 10.7 % vs. 11.1 %.

The baseline IOP was 32.6 mm Hg and 29.9 mm Hg in the dorzolamide and timolol group, respectively. Approximately half of the patients had congenital glaucoma. More patients in the dorzolamide group had Sturge-Weber syndrome than in the timolol group: 14.3% versus 7.4 %. Otherwise the distribution of glaucoma diagnoses was similar in the two groups. Age, gender, race, and proportion with prior glaucoma surgery were comparable in the two groups.

Compliance was recorded high, i.e. at least 89 % in both groups.

At week 12, the mean change in IOP was -9.4 mm Hg (-25.7 %) and -9.2 mm Hg (-30.1 %) in the dorzolamide and timolol therapy group, respectively. In the patients staying in the monotherapy regimen the mean change was -7.3 mm Hg (-20.6 %) versus -7.8 mm Hg (-24.9 %).

The observed proportion of patients with inadequate IOP control at week 12 was 46.6 % and 37.0 % in the dorzolamide and timolol group, respectively. In both groups the majority occurred during the first 3 weeks of treatment.

#### ***Rapporteur's comments***

*Additional IOP decreasing effect is clearly obtained by the addition of timolol to dorzolamide or dorzolamide to timolol, respectively, when the IOP is judged insufficiently controlled on monotherapy.*

As for the primary study endpoint, i.e. discontinuation of study therapy because of drug-related adverse experience, 1 patient (1.79 %), resulting in a 95 % CI of (0.05, 09.55) for the true proportion, discontinued in the dorzolamide group and none of the 27 patients in the timolol group (0 %, 95 % CI 0-12.8).

### Age group ≥ 2 but <6 years

A number of 101 patients were randomised, 66 to dorzolamide and 35 to timolol treatment. A number of 62 (61.4 %) completed the monotherapy phase and 19 (18.8 %) did so for the open phase. Also in this age group the proportion who discontinued was similar, namely 9.1 % versus 8.6 %.

The baseline IOP was 28.7 mm Hg and 30.3 mm Hg in the dorzolamide and timolol group, respectively. Approximately half of the patients in both groups had congenital glaucoma, and more patients in the timolol group had aphakic glaucoma, namely 28.6 % versus 16.7 %. Otherwise the distribution of glaucoma diagnoses was similar in the two groups. Age, gender, race and proportion with prior glaucoma surgery were comparable in the two groups.

Compliance was recorded high, i.e. at least 95 % in both groups.

At week 12, the mean change in IOP was -9.3 mm Hg (-25.8 %) and -7.6 mm Hg (-31.3 %) for dorzolamide and timolol, respectively.

At week 12, the mean change in IOP was -7.1 mm Hg (-23.3 %) and -7.4 mm Hg (-25.3 %) in the dorzolamide and timolol therapy group, respectively, in patients staying in the monotherapy regimen.

The observed proportion of patients with inadequate IOP control at week 12 was 33.3 % and 35.3 % in the dorzolamide and timolol group, respectively. Most cases occurred during the first 3 weeks with timolol, as opposed to with dorzolamide where the cases continued to accrue.

As for the primary study endpoint, i.e. discontinuation of study therapy because of drug-related adverse experience, 2 patients (3.03 %), resulting in a 95 % CI of (0.37, 10.52) for the true proportion, discontinued in the dorzolamide group and one (2.86 %) of the 35 patients in the timolol group, with the 95 % CI (0.07, 14.92).

**Co-rapporteur's comment:**

*For APaT analysis, regarding the monotherapy phase and the age cohort  $\geq 2$  Years but  $< 6$  Years at Week 12, the mean IOP decrease "week 12- week 0" was -7.1 mm Hg versus -7.4 mm Hg, for dorzolamide and timolol 0.5% respectively). This variation was statistically significant in both groups.*

*The 95% confidence interval determined for the difference between groups indicated a similar treatment effect for dorzolamide or timolol: dorzolamide-timolol 0.5% = 0.34 mm Hg; 95% CI= [-2.5; 3.19].*

*19/66 patients were switched to open-label concomitant therapy versus 11/35, for dorzolamide arm and timolol arm, respectively. The proportions of patients who discontinued from masked monotherapy were similar (9.1% versus 8.6%) between treatment groups.*

*Overall, 33.3 % patients (19 patients + 3 patients with IOP not controlled-Surgery) in the dorzolamide group and 35.3% in the timolol GS 0.5% group (12) had inadequate IOP control during the comparative phase.*

*At Week 12, for APaT analysis and regardless of the treatment actually received or of the possible switch to the open phase, the mean IOP decrease "week 12- week 0" was similar in both treatment arms (-7.6 mm Hg versus -9.3 mm Hg, for dorzolamide and timolol 0.5%, respectively). This variation was statistically significant in both groups.*

*The 95% confidence interval determined for the difference between groups indicated a similar treatment effect for dorzolamide or timolol: dorzolamide-timolol 0.5% = 1.70 mm Hg ; CI 95% = [-0.88 ; 4.28].*

*The small number of children in the open phase does not allow drawing any conclusion but overall, these results suggest an additional effect of adjunct therapy.*

**Rapporteur's overall conclusion on efficacy:**

*The study was not aimed to compare the two treatment groups of dorzolamide and timolol in terms of efficacy. At 12 weeks the IOP was reduced with -9.4 mm Hg (-25.7 %) in the  $< 2$  years dorzolamide group and with -9.3 mm Hg (-25.8 %) in the  $\geq 2$  but  $< 6$  years of age group. However, for 47 % and 33 % in the two age strata the IOP was reported to be inadequately controlled with dorzolamide at week 12.*

**Co-rapporteur's overall conclusion on efficacy:**

*The MAH has provided a clinical study entitled "Three month double masked active treatment controlled multicenter study of 2% dorzolamide T.I.D and of timolol maleate in Gel-Forming Solution (GS) Q.D. in pediatric patients age  $< 6$  years with elevated intraocular pressure or glaucoma (Protocol 101 and 125)".*

*Safety and efficacy of Cosopt in pediatric patients below the age of 2 years have not been studied in this pediatric MAH's trial. Therefore, the results provided by the MAH for this younger cohort of patients are not related to the use of Cosopt in pediatric patients. As a consequence, these results, which are not useful for this procedure, are neither reported or discussed in this report.*

*No literature data regarding the treatment of pediatric glaucomas with Cosopt were provided by the MAH.*

*Overall, regarding the older cohort of age ( $\geq 2$  Years but  $< 6$  Years):*

*The global analysis of the results (i.e. monotherapy + open label phase) at Week 12, for regardless of the treatment actually received or of the possible switch to the open phase showed that the mean IOP decrease "week 12- week 0" was similar in both treatment arms (-7.6 mm Hg versus -9.3 mm Hg, for dorzolamide and timolol 0.5%, respectively). This variation was statistically significant in both groups.*

*Results for the randomized monotherapy phase with dorzolamide showed that the mean IOP-lowering effect of dorzolamide at Week 12 was statistically significant reaching -7.1 mm Hg (-23.3%) in the older*

cohort ( $\geq 2$  Years but  $< 6$  Years). Therefore, the mean IOP decrease appears to be slightly higher than the effect reported in literature for long-term monotherapy with dorzolamide in adults (3-6 mm Hg). Nevertheless, similarly to what was observed in adult patients, mean IOP decreases were slightly smaller than those observed with timolol -7.4 mm Hg, for the older cohort. These results appeared to be in the same range than the IOP decreases reported by Portellos and al. in pediatric patients (-27%).

The observed proportion of patients with inadequate control of IOP at Week 12 was similar for both groups: dorzolamide 2% group: 21 (33.3%) as compared with the timolol GS 0.5% group: 12 (35.3%). The proportions of patients who discontinued from masked monotherapy were similar (9.1% versus 8.6%) between treatment groups.

30/101 children were switched to the open-label phase to be treated with Cosopt: 19/66 patients versus 11/35 patients, for dorzolamide arm and timolol arm, respectively. Therefore, the number of pediatric patients treated by Cosopt is very low. Furthermore, the results of this open label phase were pooled with the monotherapy phase and no analyses were performed examining the efficacy of the open-label combination phase. Therefore, it was difficult to identify what was exactly the additional IOP decrease in patients switched to Cosopt. Moreover, the switch to the fixed combination therapy was on the basis of clinical judgment as to when IOP was uncontrolled. No indication of the IOP levels at which this was done, has been provided. It is likely that different clinicians will have different thresholds for this change. Nevertheless, compared to monotherapy, pooled results suggest an additional IOP decrease of 0.5-2 mm Hg when Cosopt is used. This should be compared to the decrease observed in adult patients for Cosopt (i.e. 1-3 mm Hg; Merck and Co, inc; PDR). The Applicant should provide separate efficacy results for the open phase with Cosopt in the older cohort of pediatric patients.

From an efficacy viewpoint no conclusion can be drawn from these results. In line with this conclusion, the Applicant reasonably did not claim a pediatric indication for Cosopt. This seems appropriate, as data provided in the file are not sufficient to recommend a pediatric use of Cosopt in section 4.1.

However, the co-rapporteur recommends that the scarce information related to the pediatric use of Cosopt could be reflected in sections 4.2 and 5.1 of the SPC. Co-rapporteur's suggested changes are described in Annexe I attached to this report.

### **II.3.3 Clinical safety**

#### **Safety evaluation**

##### **Patient exposure:**

##### Age group $< 2$ years

In the monotherapy phase 29 patients received dorzolamide 2 % 3 drops per day for at least 61 days, and 16 patients received timolol GS 0.25 % once daily for 61 days. A number of 15 patients received 81 to 90 days and 2 got 91-100 days treatment with dorzolamide. In the open label concomitant phase 21 of the 31 patients who received open label therapy received dorzolamide 3 drops daily and timolol 0.25 % 1 drop daily for at least 41 days.

##### Age group $\geq 2$ but $< 6$ years

Forty-two patients received dorzolamide for at least 61 days, 3 drops daily, and 21 received timolol 1 drop daily for the same period. A number of 23 patients received 81 to 90 days treatment with dorzolamide and one for 91-100 days. Eighteen (18) of the 30 patients who received open label therapy combination (Cosopt®) took this medication (2 drops daily) for at least 51 days.

## **Adverse events:**

### Age group < 2 years

Discontinuations because of treatment related adverse events were 1/56 =2 %; 95 % CI 0.1-9.6 for dorzolamide and 0/27 = 0 %; 95 % CI 0-12.8 for timolol. The reported event, bradycardia, occurred during the concomitant phase and was ascribed timolol.

In the masked monotherapy phase the frequency of adverse events during monotherapy was 75 % and 63 % in the two groups, respectively; and 14 % and 15 %, respectively, was recorded as treatment related in the dorzolamide and timolol group, respectively. Serious adverse events were recorded for 11 % versus 4 % in the dorzolamide and timolol groups, respectively. No serious drug related events were reported in the monotherapy phase. Ocular symptoms emerged or worsened for 16 % in the dorzolamide group and for 26 % in the timolol group.

A total of 12.5 % and 14.8 % in the dorzolamide and timolol group reported drug related ocular symptoms with ocular injection, eye discharge, burning/stinging eyelid oedema, eyelid inflammation, itching and tearing as most common. Corneal oedema or haze was observed in 3/20 cases and 1/27 case in the dorzolamide and timolol monotherapy phase, respectively. One patient in each treatment group corresponding to 1.8 % and 3.7 % in the dorzolamide and timolol group, respectively, experienced worsening in visual acuity at week 12. The MAH does not distinguish clearly between ocular adverse events reported in the monotherapy and open label phases.

For two patients a clinically significant (predefined as  $\leq 78$  % of the lower limit of normal value) CO<sub>2</sub> value was observed, one in the open label concomitant phase, the other, however, in the monotherapy timolol phase.

### ***Rapporteur's comment:***

*A risk for metabolic acidosis exists with the topical application of dorzolamide.*

In the concomitant phase 73 % and 78 % in the group initially randomised to dorzolamide and to timolol, respectively, reported one or more adverse events. The figures for reported drug related adverse events were 27 % versus 11 %, respectively. Serious clinical adverse experiences were recorded for 22 % versus 5 % in the group initially randomised to dorzolamide and to timolol, respectively. One adverse event, bradycardia was determined to be related to timolol.

### Age group $\geq 2$ but <6 years

Discontinuation because of treatment related adverse events were 2/56=3 %; (95 % CI 0.4-10.5) for dorzolamide and 1/35=3 %; 95 % CI 0.1-14.9 for timolol. The reasons were eye pain, ocular injection, burning/itching with dorzolamide and ocular injection with timolol.

In the masked monotherapy phase the frequency of adverse events during monotherapy was 76 % and 69 % in the two groups, respectively; and 26 % and 23 %, respectively, was recorded as treatment related in the dorzolamide and timolol group, respectively. Ocular symptoms emerged or worsened for 27 % in the dorzolamide group and for 29 % in the timolol group.

No cases of drug related serious adverse were reported. A total of 19.6 % and 18.5 % in the dorzolamide and timolol group reported drug related ocular symptoms with ocular injection, eye discharge, burning/stinging eyelid oedema, eyelid inflammation, itching and tearing as most common. For 3 patients (4.5 %) and 2 patients (5.7 %) in the dorzolamide and timolol group, respectively, worsening in visual acuity at week 12 was recorded. No cases of serious clinical adverse events were considered to e drug related.

In the combination phase 17/30 (56.7 % had a clinical adverse experience. No serious adverse events were reported. Drug related adverse events were predominantly ocular with ocular injection, burning/stinging eyelid oedema, eyelid inflammation and eye irritation being most frequent.

**Rapporteur's comment:**

*These reports are not considered unexpected.*

**Co-rapporteur's comment:**

*In the age cohort  $\geq 2$  years and  $< 6$  years, 2 patients of 66 initially randomized in dorzolamide group, and 1 patient of 35 initially randomized to the timolol group discontinued due to drug-related adverse events. All effects were effects ranged in special sense in the MedDRA classification, and were principally eye pain, ocular injection, burning/stinging. These effects are listed in the dorzolamide and timolol SPC. All these effects were not serious.*

*In the age cohort  $\geq 2$  years and  $< 6$  years, 4 patients discontinued for clinical adverse experience, 2 patients were randomized to dorzolamide (3.0%) and 2 patients to timolol group (5.7%). A greater percentage of patients in timolol group discontinued due to adverse experiences, but this was not significantly different.*

*In addition, 8 patients initially randomized in the dorzolamide group and 3 patients in the timolol group discontinued for IOP non-controlled before surgery. It seems to be worth in the dorzolamide group than in the timolol group. The Applicant should comment.*

*The percentages of patients with clinical adverse experiences were similar in both groups and in both age cohort.*

*In the age cohort  $\geq 2$  years and  $< 6$  years, more patients in the dorzolamide group reported vomiting (10.6% vs 5.7%) and headache (10.6% vs 5.7%). The MAH should comment.*

*The majority of drug-related adverse experiences were in the special sense body system:*

*Of the 17 patients (25.8%) initially randomized in the dorzolamide group who have drug related clinical adverse experiences, 15 (22.7%) experienced adverse events in special senses body system (burning/stinging, eyelid inflammation, ocular injection, eye pain).*

*In timolol group, among the 9 (25.7%) patients who experienced drug related clinical adverse experiences, 8 (22.9%) had adverse events in special senses body system (burning/stinging, ocular injection, eye pain, ptosis). These adverse events were ocular discomfort or irritation.*

*The percentages of patient with drug related clinical adverse experiences were similar in both groups.*

*For the age cohort  $\geq 2$  years and  $< 6$  years, all effects were systemic effects in 3 dorzolamide patients and 1 timolol patient: urinary infection, otitis, anorexia and stomatitis for patients who were randomized in the dorzolamide group, and gastroenteritis for the timolol patients. None of the serious clinical adverse experiences was determined to be drug related by the MAH.*

*There were no serious clinical adverse experiences reported during the combination therapy phase. In the cohort  $> 2$  years, the MAH should submit the narratives or CIOMS of all serious cases.*

*For the age cohort  $\geq 2$  years and  $< 6$  years, 19 patients (28.8%) in the dorzolamide group and 13 (37.1%) in the timolol group reported emergent or worsening ocular symptoms. As in the age cohort  $< 2$  years, a greater percentage of patients in the timolol group reported eye discharge, ocular injection, and burning/ stinging.*

Other safety measurements were: Changes in vital signs, alertness and corneal diameter were not noteworthy in the two age strata.

No deaths were reported in the study.

***Co-rapporteur's comment:***

*All vital signs at baseline were similar in both treatment groups, in all cohort age and in monotherapy and combination therapy phase.*

*In the age cohort  $\geq 2$  years but  $< 6$  years, in combination therapy phase with Cosopt, the decrease of  $-10.8$  in mean change for pulse rate in the dorzolamide initially randomized group was greater than in the timolol initially randomized group ( $-1.8$ ).*

**Laboratory findings**

Age group  $< 2$  years

No laboratory adverse experiences were reported for the monotherapy phase. One case of reported a decreased total CO<sub>2</sub> in the open label concomitant phase.

Age group  $\geq 2$  but  $< 6$  years

One patient had a decreased PCO<sub>2</sub> (measured in error of the scheduled total PO<sub>2</sub>). In the open label combination phase no laboratory adverse events were reported.

***Co-rapporteur's comment:***

*As dorzolamide is a topical carbonic anhydrase inhibitor for the treatment of elevated intraocular pressure (IOP), in order to explore the known adverse events acid-base disturbances, the chemistry laboratory test total CO<sub>2</sub> was performed at study day 1 and week 12. There were no laboratory adverse experiences reported for the combination phase.*

**Long-term safety data; effect on development (growth, motor, mentally, sexually) and cognition**

Such data are not available.

***Rapporteur's comment:***

*Considering the presumed low systemic exposure the lack of any information on effect on development (growth, motor, mentally, sexually) and cognition would be acceptable.*

Merck & Co., Inc World wide Adverse Experience System (WAES) for Cosopt

As for the WAES, 7 reports have been identified of which 2 were serious: One 4 year old patient was hospitalised with hypertension and had paroxysmal abdominal pain, several other medication was concomitantly administered; however, no BP-measurements were reported. The other serious report encompassed corneal oedema and corneal opacity, which recovered after stopping the administration of Cosopt. Corneal oedema is a labelled event with the combination. The rest of the reports were eye swelling, pruritus, rash and alopecia, all of which are well known with the use of Cosopt.

**Rapporteur's comment:**

*No separate prospective study to evaluate efficacy and safety of Cosopt in a paediatric population has been conducted. The submitted data derive from an open treatment period following a double-blind randomised treatment phase, to which the patients were switched if the monotherapy was insufficient in terms of controlling the IOP during the double-blind monotherapy phase.*

*Basically, the only relevant data pertain to the number of patients who were switched to the open label phase to be treated with Cosopt. This involves only patients  $\geq 2$  but  $< 6$  years of age. These patients are stated to encompass 30 subjects of whom 18 were treated for at least 51 days and 6 were treated for 1 day (one dose). A number of 17 (56.7 %) had clinical adverse experience, of which none were serious. One patient had fever, upper respiratory infection and ocular injection. Five patients (16.7 %) reported an emergent or worsening ocular symptom, most frequently ocular injection, burning/stinging, eye discharge and tearing. However, no patients discontinued due to adverse events, and no deaths were reported during the use of Cosopt. Laboratory adverse events in the period of Cosopt therapy were unremarkable, in particular no changes in  $CO_2$  were reported. For vital signs no unexpected findings were reported. Patient alertness, corneal diameter and visual acuity were also unremarkable.*

**Co-rapporteur's comment:**

*Seven reports were received by the MAH, among them 2 were serious (Corneal oedema and Corneal opacity and hypertension).*

*The MAH should provide the narratives of the 2 serious cases.*

**Rapporteur's overall conclusion on safety:**

*A limited number of patients in two age groups  $< 2$  years and  $\geq 2$  but  $< 6$  years have been assessed in a short trial. The discontinuation rate because of a drug related adverse event – which was the primary endpoint - was 2 % (CI: 0.1 %-9.6 %) and 3 % (CI: 0.4 % -10.5 %) in the two age groups, respectively, caused by eye pain, ocular injection, burning/stinging eye and eye itching. This pattern is consistent with what is known from adult patients. For 2 patients, however, corneal opacity was reported. Approximately one forth of the patients had drug related adverse experiences, predominantly ocular, with 15-18 % in the double-masked monotherapy phase and 11-27 % in the concomitant open label phase. Only one serious drug related adverse event was reported in the study: bradycardia, which was considered related to timolol. In the WAES database one case of serious corneal oedema and corneal opacity was reported. A signal of metabolic acidosis was detected in the WAES database, however, in the submitted clinical trial no unexpected adverse event findings neither in nature or frequency were suspected. It is advised that special attention should be paid to any possible coming reports of corneal opacity.*

**Co-rapporteur's overall conclusion on safety**

*The primary objective of this study was to document an acceptable safety profile for dorzolamide in patients 1 week to  $< 2$  years of age and in patients  $\geq 2$  years but  $< 6$  years of age with elevated IOP or glaucoma. The proportion of patients who discontinued therapy due to a drug-related adverse experience prior to completing 3 months of therapy was chosen to be statistically less than 25 %. However, no justification is available regarding the choice of this wide limit, which appears artificial and likely motivated by the understandable Applicant's objective of reaching positive results from a study that includes a limited number of pediatric patients.*

*Nevertheless results show that:*

*-3 patients from the age cohort  $< 2$  years, respectively one randomized to dorzolamide (1.8%) and two in timolol group (7.4%), discontinued for clinical adverse experience;*

- 4 patients from the age cohort  $\geq 2$  years and  $< 6$  years, respectively 2 randomized to dorzolamide (3.0%) and 2 in timolol group (5.7%), discontinued for clinical adverse experience.

However, no patient in the combination phase with Cosopt, discontinued due to drug-related adverse experience.

In both cohorts, a greater percentage of patients in timolol group discontinued due to adverse experiences, but this was not significantly different.

No safety concerns were observed from this trial in pediatric patients.

Of the 101 patients (age  $\geq 2$  but  $< 6$  years) initially randomized to either Dorzolamide 2.0% or Timolol 0.5%, 30 patients were switched to the open-label administration of Dorzolamide 2.0%/Timolol 0.5% combination (Cosopt).

Nineteen of the thirty patients completed the open-label phase (12 patients in initially randomized dorzolamide and 7 in timolol). Three (10%) of the thirty patients experienced a drug related adverse experience. The adverse experiences reported were 1 each of cough, ocular injection, and ocular burning/stinging. No serious adverse experiences were reported in the combination.

Overall, the most common adverse events reported were in the body systems of digestive, respiratory, and special senses. The most common drug-related adverse experiences reported for dorzolamide were ocular burning/stinging and ocular injection in patients  $\geq 2$  years but  $< 6$  years of age.

For the most part, the safety profile of dorzolamide in pediatric patients reflects that seen in adults, except for digestive and respiratory disorder. Local side effects were the most common drug-related adverse experiences in adults and children. In older children ( $\geq 2$  years but  $< 6$  years), the most common ocular adverse experience was ocular burning/stinging.

Data from the clinical trial (100/125), corroborated with data from post-marketing WAES database support that there are no safety concern with Cosopt in children  $\geq 2$  but  $< 6$  years of age. Of the 3 reports on serious adverse events listed in the WAES report, only the incidence of hypertension would not be expected from this product. The patient who experienced hypertension was taking other topical medications for glaucoma (Travoprost). All investigational work-up was negative and no blood pressure measurements were recorded. The patient subsequently recovered with treatment. The relationship of the event to the use of Cosopt was not established and the patient continued to receive Cosopt.

No younger patient ( $< 2$  years) received the combination Dorzolamide 2.0% - Timolol 0.5% (Cosopt).

Twice daily administration of Dorzolamide 2.0% - Timolol 0.5% ophthalmic solution (Cosopt) was generally well tolerated in glaucomatous and ocular hypertensive pediatric patients  $\geq 2$  but  $< 6$  years of age.

Therefore, according to the pediatric study condition, the primary objective to demonstrate an acceptable safety profile was strictly reached. But, the occurrence of uncommon adverse events cannot be ruled out, in particular the risk of acid-base disturbances in relation with the pharmacodynamic profile of dorzolamide.

## REQUEST FOR SUPPLEMENTARY INFORMATION

### Major objections

None

### Other concerns

#### Clinical safety

##### ***Question 1 (Co-rapporteur):***

In the age cohort  $\geq 2$  years but  $< 6$  years, 8 patients initially randomized in the dorzolamide group and 3 patients in the timolol group discontinued for IOP non-controlled before surgery.

The Applicant should comment.

##### ***Question 2 (Co-rapporteur):***

The percentages of patients with clinical adverse experiences were similar in both groups and in both age cohort. In the age cohort  $\geq 2$  years and  $< 6$  years, more patients initially in the dorzolamide group reported vomiting (10.6% vs 5.7%) and headache (10.6% vs 5.7%)

The MAH should comment the difference in the both groups (dorzolamide and timolol).

##### ***Question 3 (Co-rapporteur):***

A greater proportion of patients who initially randomized in dorzolamide group had a drug-related clinical adverse experience compared with those randomized to timolol. The MAH should comment.

##### ***Question 4 (Co-rapporteur):***

In the clinical trial, the MAH should submit the narratives or CIOMS of all serious cases.

##### ***Question 5 (Co-rapporteur):***

In the post-marketing data, the MAH should provide line listing of all adverse events and narratives or CIOMS of all serious adverse events.

*(Co-Rapp)*

#### Clinical efficacy

##### ***Question 6 (Co-rapporteur):***

In the age cohort  $\geq 2$  years but  $< 6$  years, 30 children were switched to Cosopt fixed combination (dorzolamide plus timolol), however the results of this open label phase were pooled with the monotherapy phase. Therefore it was difficult to identify what was exactly the additional IOP decrease when dorzolamide was used in adjunct to timolol. Moreover, the switch to open label therapy was on the basis of clinical judgment as to when IOP was uncontrolled. No indication of the IOP levels at which this was done, has been provided. It is likely that different clinicians will have different thresholds for this change. Nevertheless, these results suggest an additional IOP decrease of 0.5-2 mm Hg. The Applicant should provide the open phase results for Cosopt and explain why these results were not presented separately in the pediatric file.

##### ***Question 7 (Rapporteur):***

The outcome of IOP should be provided for patients treated with Cosopt in the open label combination phase in a survey, to enable distinction between results from all-population results (i.e. patients continuing in the monotherapy phase and patients switched to combination treatment in the open label phase).

***Question 8 (Co-rapporteur):***

IOP measurement protocol: although attempts were made to have each patient's IOP measurements taken at approximately the same time at each clinical visit, no relevant information is provided in the protocol regarding the technique used in children for IOP measurement. It is highlighted in the file that the method of measurement was left at the physicians' discretion among the 3 listed in the protocol (Goldmann, Tonopen, or Perkins tonometry). Therefore, this suggests that no standardized IOP measurement method between centers (US or non-US) has been applied. In addition, no information is available about the general anesthesia procedure applied while it is usually required to measure the eye pressure more accurately when an ophthalmologist suspects the pediatric glaucoma condition. Since the technique chosen for general anesthesia may widely affect the IOP values, this is of importance especially in case of a multicenter study.

The Applicant should explain why a common protocol for IOP measurement and for general anesthesia when required is lacking or not available in the file. Moreover, the Applicant should discuss how this might affect results on IOP measurements in pediatric population.

## **ASSESSMENT OF REQUESTED SUPPLEMENTARY INFORMATION**

### **Clinical safety**

**Question 1:**

**Response:**

This study was not designed to address to effectiveness of either drug in controlling IOP, but rather to expose a sufficient number of children to Trusopt to discern whether there are any safety concerns with its use in this population. However, the number of patients in the dorzolamide group was approximately twice that in the timolol group, resulting in percentages (versus counts) that are roughly similar. Congenital and pediatric glaucoma are difficult to control with medical therapy alone, indeed, congenital glaucoma is a surgical condition. It is not unusual for patients to require surgery for these conditions regardless of what the initial therapy is.

**Rapporteurs' comments:** *Issue resolved.*

**Question 2:**

**Response:**

For each of the adverse experiences identified above, pairwise comparisons between the treatment groups were performed using Fisher's exact test (two-sided). The pairwise tests were for exploratory purposes and no multiplicity adjustment was applied. Therefore, significant p-values found in this context should not be interpreted, in isolation, as an indication of a true treatment effect, either positive or negative. Despite the fact that no multiplicity adjustment was applied for the multiple pairwise tests, neither of the pairwise comparisons were statistically significant, indicating that there are no differences between the treatment groups with respect to the incidence of vomiting (p=0.491) or headache (p=0.491) in the age cohort  $\geq 2$  years and  $< 6$  years.

**Rapporteurs' comments:** *The observed numerical difference is not likely to be of major clinical importance.*

*Issue resolved.*

**Question 3:**

**Response:**

Of the 83 patients in the age cohort < 2 years, 19 (22.9%) reported one or more clinical adverse experiences determined by the investigator to be drug-related: 14/56 (25.0%) in the dorzolamide group and 5/27 (18.5%) in the timolol group. The difference in proportions between the 2 treatment groups (dorzolamide minus timolol) was 6.5, with a 95% CI of (-16.1, 30.5) and an associated p-value=0.599, indicating that there is no difference between the treatment groups with respect to the incidence of drug-related adverse experiences in the age cohort < 2 years.

Of the 101 patients in the age cohort  $\geq$  2 years and < 6 years, 26 (25.7%) reported one or more clinical adverse experiences determined by the investigator to be drug-related: 17/66 (25.8%) in the dorzolamide group and 9/35 (25.7%) in the timolol group. The difference in proportions between the 2 treatment groups (dorzolamide minus timolol) was 0.0, with a 95% CI of (-20.2, 21.9) and an associated p-value>0.999, indicating that there is no difference between the treatment groups with respect to the incidence of drug-related adverse experiences in the age cohort  $\geq$  2 years and < 6 years.

**Rapporteurs' comments:** *The observed numerical difference is not likely to be of major clinical importance.*

*Issue resolved.*

**Question 4:**

**Response:**

The CIOMS reports of all of the serious cases from the clinical trials can be found in Attachment I.

**Rapporteurs' comments:**

*The MAH has submitted the CIOMS of 4 patients (WAES nos. 01081149, 0206CZE00001, 0206CZE00004, and 01041878). The age of the patients was 30 months, 35 months, 24 months, and 3 years, respectively.*

*All of these patients had other diseases (congenital urological system defect and chronic recurrent history of infections, trabeculectomy and conjunctivitis infective and stenosis of lacrimal sac, epilepsy and sturge-Weber syndrome and hyperopia and amblyopia and hemiparesis and cerebral atrophy) than their glaucoma, which could explain the information in the submitted Suspect Reaction Report Forms. The investigators did not regard any of these cases related to study medication, which is likely true, based on review of the reports.*

*Issue resolved.*

**Question 5:**

**Response:**

The CIOMS reports of all of the serious cases from post-marketing data can be found in Attachment II. Line listing of all adverse events from post-marketing data are provided in Attachment III.

**Rapporteurs' comments:**

The MAH has submitted CIOMS of patient WAES 0402FRA00047 and patient WAES 99100603 who had respectively hypertension and corneal oedema and corneal opacity. The first one, was a 4 year old male child who has been hospitalized for paroxysmal abdominal pain and hypertension. Therapy with dorzolamide + timolol was continued. The patient was placed on therapy with antalgic drug and nicardipine. The patient recovered. The remaining patient, was a 7 month male patient, who developed corneal edema and corneal opacity. The therapy with dorzolamide + timolol was discontinued and the patient recovered. The events of both cases were considered to be related to the use of Cosopt by the ophthalmologist.

Furthermore, a line listing was submitted with 7 reports of adverse events: 2 serious (both seen above) and 5 non serious (vision blurred, alopecia, vitreous floaters, eye pain, skin eruption and swollen eyes).

No new safety concern was found in this post-marketing data.

Issue resolved

**Clinical efficacy****Question 6+7:****Response:**

An analysis of IOP reduction during the open-label phase of the study was not performed because such an analysis would not be appropriate due to the fact that the patients whose study therapy was changed to the dorzolamide/timolol fixed combination therapy were not a randomized population. The study therapy of the patients was changed to combination therapy at the discretion of the investigator during the study, rather than these patients being identified prior to the study and subsequently being randomized to 1 of the 2 initial treatment groups. The study was not designed to evaluate the additional IOP effect of combination therapy following initial therapy with either dorzolamide or timolol.

Table 1 displays IOP summary statistics at baseline, the end of the monotherapy phase and the end of the combination therapy phase of the study for patients in the age cohort  $\geq 2$  years but  $< 6$  years. However, as mentioned above, an analysis of these summary statistics would not be appropriate.

Table 1 IOP<sup>†</sup> (mmHg) Summary Statistics (All-Patients-Treated Analysis/Last-Observation-Carried-Forward Approach)—Study Eye (Age Cohort  $\geq 2$  Years but  $< 6$  Years)

Treatment	N	Baseline			End of Monotherapy Phase			End of Combination		
		Mean	SD‡	Median	Mean	SD‡	Median	Mean	SD‡	Median
Dorzolamide 2%	19	31.2	8.2	28.0	26.8	4.0	26.5	25.1	6.5	25.0
Timolol 0.5% GS	11	34.4	7.2	33.0	29.0	4.2	29.0	23.3	6.6	23.3

† IOP = Intraocular pressure. ‡ SD = Standard deviation.

**Rapporteurs' comments:** *The MAH's argument that an analysis would not be appropriate because the population was not randomised is not valid. An assessment of any additional efficacy with the combination in patients not sufficiently controlled on monotherapy would have been informative. However, at his point no further exploration is meaningful.*

*Issue partly resolved, no further action should be taken.*

### **Question 8:**

#### **Response:**

Since this was primarily a safety study, it was acceptable to allow investigators to use the IOP measurement technique with which they were most comfortable when dealing with a pediatric population where consistently reproducible measurements are needed. IOP measurements in children are difficult to obtain in the same manner as adults (i.e. at a biomicroscopic slit lamp with Goldmann applanation tonometry) due to movements, crying, and holding one's breath. Both Perkins and tonometry and the Tonopen are accepted and reasonable methods for collecting IOP data. The value of repetition with the same calibrated instrument is more important than the method itself.

It is true that general anesthesia may affect IOP measurements. Most anesthetics reduce IOP. The possible exceptions are ketamine and succinylcholine, which may cause extraocular muscle fasciculations potentially increasing IOP readings. These two agents are not commonly used for examination under anesthesia (EUA).

General anesthesia was not included in the protocol as it was not felt ethical to subject patients to general anesthesia for the purposes of this clinical study. If a study visit coincided with an EUA that had been scheduled for another purpose, then information from the EUA could be used as study data. This restriction was made clear to investigators prior to study initiation; investigators who were not comfortable with this did not participate. Moreover, EUAs generally are not performed to monitor IOP, but rather to check suspected glaucomatous disease or disease progression by examination of the optic nerve head and other ocular signs. The choice of general anesthesia is individualized and is not part of a protocol for this condition.

One should be assured that the IOP measurements of the pediatric population in this study were taken with precautions of properly calibrated instruments; consistent use of the same measurements device/technique for each patient; avoidance of measurements taken under general anesthesia unless done for other predetermined medical reasons.

#### **Rapporteurs' comments:**

*In one hand, the Applicant confirms that no standardisation was attempted regarding IOP measurement and that the choice of general anesthesia was individualized and was not part of the protocol.*

*In the other hand, this study was not primarily an efficacy study and no paediatric indication was claimed for Cosopt.*

*Issue resolved*

## **OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**

Cosopt eye drops, solution are currently approved for the treatment of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or pseudoexfoliative glaucoma when topical beta-blocker monotherapy is not sufficient. As a part of the EU work sharing project in the assessment of already available paediatric data for existing products, the MAH has submitted available paediatric data for Cosopt.

The MAH has provided a clinical study entitled “Three month double masked active treatment controlled multicenter study of 2% dorzolamide T.I.D and of timolol maleate in Gel-Forming Solution (GS) Q.D. in pediatric patients age <6 years with elevated intraocular pressure or glaucoma (Protocol 101 and 125)”.

The primary objective of this study was to document an acceptable safety profile for dorzolamide in patients 1 week to < 2 years of age and in patients  $\geq 2$  years but < 6 years of age with elevated IOP or glaucoma, whereas the IOP-lowering effect of dorzolamide 2% was only a secondary objective of this paediatric study.

The available data for Cosopt pertain from the open label phase following a masked double-blind controlled study with Trusopt. A total of 30 patients in the age  $\geq 2$  but < 6 years were exposed to Cosopt.

From an efficacy viewpoint no conclusion can be drawn from these results. In line with this conclusion, the Applicant did not claim a paediatric indication for Cosopt. This seems appropriate, as data provided in the file are not sufficient to recommend a paediatric use of Cosopt in section 4.1.

Both the Rapporteur and Co-rapporteur consider that the provided safety data support an inclusion of information of Cosopt in a paediatric glaucoma population in the paediatric population  $\geq 2$  but < 6 years of age.

## **IV. PROPOSED CHANGES IN THE SPC**

### **Section 4.2**

*Efficacy in paediatric patients has not been established.*

*Safety in paediatric patients below the age of 2 years has not been established. (For information regarding safety in paediatric patients  $\geq 2$  and  $< 6$  years of age, see section 5.1)*

### **Section 4.4**

*Paediatric Use*

*See section 5.1.*

### **Section 5.1**

*Paediatric use*

*A 3 month controlled study, with the primary objective of documenting the safety of 2% dorzolamide hydrochloride ophthalmic solution in children under the age of 6 years has been conducted. In this study, 30 patients under 6 and greater than or equal to 2 years of age whose IOP was not adequately controlled with monotherapy by dorzolamide or timolol received COSOPT in an open label phase. Efficacy in those patients has not been established. In this small group of patients, twice daily administration of COSOPT was generally well tolerated with 19 patients completing the treatment period and 11 patients discontinuing for surgery, a change in medication, or other reasons.*