

**Direction de l'Évaluation
des Médicaments et des Produits Biologiques**

**PAEDIATRIC PUBLIC ASSESSMENT REPORT
EU Work Sharing Procedure – Assessment of
Paediatric Data**

TRUSOPT 2 %, eye drops solution

Dorzolamide hydrochloride

Applicant: Merck Sharp & Dohme

Date of the PaedPAR: February 2008

Information about the initial procedure:

Rapporteur	<i>France</i>
Co- Rapporteur	<i>Denmark</i>
Paediatric assessment report Procedure start date :	<i>28 October 2005</i>
Deadline for (Co)-Rapporteur's preliminary report	<i>12 January 2006</i>
Clock-stop	<i>2 February 2006</i>
Deadline for Rapporteur's final report	<i>19 June 2006</i>
Deadline for member states final comments	<i>9 July 2006</i>
End of procedure	<i>21 September 2006</i>

1. INTRODUCTION

Trusopt 2% was listed under the "EU worksharing project in the assessment of available paediatric data". Consequently, as a part of this procedure, the Applicant has submitted the requested paediatric file for Trusopt 2% eye drops, solution.

The procedure started on October 28, 2005. France and Denmark have been appointed as Rapporteur and Co-Rapporteur, respectively.

This paediatric dossier consisted of the following documentation:

- A three-month double-blind, multicentre, controlled study comparing 2% dorzolamide, eye drops, solution, and of 0.5% timolol, in paediatric patients of less than 6 years of age with elevated intraocular pressure or glaucoma
- A cumulative safety review of all reports from Merck & Co., Inc. WAES (Worldwide Adverse Experience System) database, covering the product's use in patients of less than 18 years of age;
- Published literature on glaucoma in the paediatric population .

Based on the dossier review, the paediatric clinical trial was considered not sufficient to justify a formal therapeutic indication in children,. Nevertheless, some statements to be included in the current summary of product characteristics (SPC) were proposed regarding the product's use in children.

In parallel to the present procedure, Cosopt eye drops, solution (a fixed combination of 2% dorzolamide and 0.5% timolol from Laboratoire Merck Sharp & Dohme, registered through mutual recognition procedure in 1998), has been also listed under the EU worksharing assessment procedure. Denmark and France have been appointed as Rapporteur and Co-Rapporteur, respectively.

No separate prospective study to evaluate the efficacy and safety of Cosopt in the paediatric population has been conducted. The submitted data were derived from the open phase of the study carried out for Trusopt. Patients were switched to add-on therapy if the monotherapy with Trusopt 2% vs timolol 0.5% was insufficient in terms of controlling the intraocular pressure.

The corresponding public assessment report (PAR) was written by Denmark.

About the product

Trusopt 2% eye drops solution (dorzolamide hydrochloride) was the first marketed topical carbonic anhydrase inhibitor.

Dorzolamide is a potent inhibitor of human carbonic anhydrase II, i.e. an enzyme found in many tissues of the body including the eye. Following topical ocular administration, dorzolamide reduces elevated intraocular pressure, whether or not associated with glaucoma.

Trusopt 2% eye drops, solution has been registered through the Ex-Concertation Procedure (N° FR/H/70/01) on November 1994. It was first registered in 12 European member states. The marketing authorisation was renewed twice through a mutual recognition procedure (MRP) in 2000 and 2005, and finally extended to additional European member states.

Trusopt 2% eye drops, solution is currently approved worldwide.

Trusopt is indicated as second line treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma, i.e.:

- as adjunctive therapy to beta-blockers,
- as monotherapy in patients unresponsive to beta-blockers or in whom beta-blockers are contraindicated,

in the treatment of elevated intra-ocular pressure in:

- ocular hypertension,
- open-angle glaucoma,
- pseudoexfoliative glaucoma.

When used as **monotherapy**, the dose of dorzolamide is one drop in the conjunctival sac of the affected eye(s), three times daily.

When used as **adjunctive therapy** with an ophthalmic beta-blocker, the dose is one drop in the conjunctival sac of the affected eye(s), two times daily.

Background on congenital and juvenile glaucoma:

Glaucoma in childhood consists of a group of various blinding conditions which have one common feature of raised intraocular pressure (IOP). The classification is broadly grouped into either congenital disorders (primary developmental anomalies present in the drainage angle or secondary to other ocular or other developmental anomalies), or juvenile onset disorders.

If the condition is suspected by an ophthalmologist, the child is usually examined under general anaesthesia in order to measure the eye pressure accurately, examine the angle of the eye, and evaluate the optic nerve.

Treatment is primarily surgical with medical treatment used as an adjunct. Chronic use of medical therapy is often of concern because of systemic side effect or non adherence to treatment.

Paediatric glaucomas present with higher baseline IOP values than adult glaucoma and pertain to different causes, which may affect differently the treatment efficacy.

Clinical experience with topical beta-blockers (e.g.; timolol) in childhood glaucoma is less limited than for other active compounds. Timolol is often used as first line topical therapy when no contraindications, such as asthma, exist and therefore can be considered as a treatment reference validated by its use in children.

Systemic anhydrase inhibitors (acetazolamide) have been used as an acute treatment for the management of paediatric glaucoma. However, these drugs are not well tolerated by many children. Indeed in the paediatric population, several adverse events are typically associated with the use of oral anhydrase inhibitors: risk of metabolic acidosis, hypokaliemia, fatigue, paresthesias, tinnitus, nausea, anorexia and gastrointestinal disturbances.

Therefore, local anhydrase inhibitors (dorzolamide) were proposed as a safer option for the treatment of childhood glaucoma. Clinical opinion is that topical carbonic anhydrase inhibitors appear to be less effective than beta blockers, but safe, although associated with local irritation. Consequently, they are

considered useful as an adjunctive therapy to beta-blockers or as monotherapy in patients unresponsive to beta-blockers or in whom beta-blockers are contraindicated.

Prostaglandins are not considered as effective in childhood glaucoma as in adults, but may have a role in some patients with juvenile open angle glaucoma, or with aphakic glaucoma.

Alpha-adrenergic agonists are considered to display serious, potential systemic side effects, which preclude their use in neonates and young infants.

2. QUALITY ASPECTS

NA

3. NON-CLINICAL ASPECTS

NA

4. CLINICAL ASPECTS

4.1 Introduction

In the recent years, the European Community has supported effort to increase the submission of clinical studies conducted in children, in order to make available pediatric clinical information on drugs, with data previously submitted to the Food and Drugs Administration (FDA) in the USA.

4.2 Pharmacokinetic (PK) aspects:

No additional data were provided in the paediatric dossier regarding clinical pharmacokinetic.

Unlike oral carbonic anhydrase inhibitors, topical administration of dorzolamide hydrochloride allows the drug to exert its pharmacological effect directly in the eye at substantially lower doses, and therefore with less systemic exposure. In clinical trials carried out in adults, this resulted in a IOP reduction, without acid-base disturbances or alterations in electrolytes, which are associated with oral carbonic anhydrase inhibitors.

4.3 Pharmacodynamic (PD) aspects:

No additional data were provided in the paediatric dossier regarding clinical pharmacology.

4.4 Efficacy and safety in the paediatric population;

Previous paediatric experience:

Experience with dorzolamide, in few paediatric patients with glaucoma, came from six published references. No numerical figures on the IOP values were provided in these studies, except for the 6-month study by Portellos et al, in which an IOP decrease of 27% was reported. These reports suggested that dorzolamide decreases IOP with an acceptable safety profile.

Paediatric study submitted by the Applicant under the "EU worksharing project in the assessment of available paediatric data" procedure:

The only study submitted was conducted by Merck in response to the Written Request for paediatric data issued by the FDA. It was conducted under Good Clinical Practice.

The study was a randomised, 3-month, double-masked, active-controlled, multicentre study (protocole N°100/125) aiming to investigate the safety and the ocular hypotensive effect of dorzolamide.

Dorzolamide 2 % was administered topically three times a day (t.i.d) in patients younger than 6 years of age with elevated IOP or glaucoma. The study population was divided in two age strata (<2 years and ≥2 years but <6 years)

Timolol maleate gel-forming solution (timolol GS) once daily (q.d.) was the active treatment control: timolol GS 0.25% and timolol GS 0.5% were used for patients < 2 years and for patients \geq 2 years but < 6 years, respectively

Patients were randomised 2:1 with respect to dorzolamide: timolol GS therapy.

The IOP-lowering effect of dorzolamide 2% was only a secondary objective of this paediatric study when safety was the primary one.

Inclusion criteria encompassed intraocular pressure (IOP) \geq 22 mm Hg in patients with suspected or confirmed glaucoma.

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 medications were discontinued at a pre-study evaluation visit and the duration of any wash-out period was left to the Investigator's discretion according to appropriate guidance for wash-out periods.

If IOP was inadequately controlled on monotherapy, a change was made to open-label concomitant/combination therapy, as follows:

- concomitant therapy of dorzolamide 2 % t.i.d. and timolol GS 0.25 % q.d for patients < 2 years old,
- or combination therapy of dorzolamide 2 % / timolol 0.5 % (Cosopt), twice daily (b.i.d.), for patients \geq 2 but <6 years old.

Visits were scheduled at weeks 1, 4, and 12, and 2 weeks after stopping the study medication. At each study visit, it was to be decided if the patient should continue with masked monotherapy, or if he should switch to the open-label concomitant/combination therapy.

Summary of efficacy results in paediatric study:

One hundred eighty-four patients were randomized into the study at 29 study sites (16 U.S. and 13 International sites).

■ Age cohort <2 years:

A total of 83 patients were randomized (56 patients to dorzolamide 2% therapy and 27 to timolol GS 0.25%). This cohort included patients from 1 week to 23 months of age.

In this cohort, the mean baseline IOP was higher in the dorzolamide group than in the timolol group (32.6 mm Hg versus 29.9 mm Hg, respectively).

■ Age cohort \geq 2 years but <6 years:

A total of 101 patients were randomized (66 patients to dorzolamide and 35 to timolol). The mean age of paediatrics was about 3.5 years.

The mean baseline IOP was higher in the timolol group than in the dorzolamide group (30.3 mm Hg versus 28.6 mm Hg, respectively).

Approximately half of the patients in both age cohorts were diagnosed with congenital glaucoma. The other common etiologies were Sturge Weber syndrome, iridocorneal mesenchymal dysgenesis, aphakic patients.

● **Efficacy results from the randomized monotherapy phase:**

Overall, efficacy results in paediatric patients suggested that the mean IOP decrease observed in the dorzolamide group was comparable to that observed in the timolol group, even if there was slight numerical advantage in favour of timolol:

At week 12, the mean IOP-lowering effect of dorzolamide was statistically significant in both cohorts of age reaching -7.3 mm Hg (-20.6%) and -7.1 mm Hg (-23.3%) in the younger cohort (<2 years) and in the older cohort (\geq 2 Years but <6 Years), respectively.

The mean IOP decrease appeared 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 (i.e. -7.8 mm Hg and -7.4 mm Hg, for the younger cohort and for the older cohort, respectively).

The 95% confidence interval (CI) determined for the difference between groups indicated a similar treatment effect for dorzolamide or timolol either for the younger cohort (dorzolamide-timolol 0.25% = 0.57 mm Hg; 95% CI= [-3.39, 4.54]), and for the older cohort (dorzolamide-timolol 0.5% = 0.34 mm Hg; 95% CI= [-2.5; 3.19]).

For the younger cohort, the observed proportion of patients with inadequate control of IOP at Week 12 was greater for the dorzolamide 2% group (n=27 - 46.6%) as compared with the timolol group (n=10- 37.0%).

For the older cohort, 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 (n=12 - 35.3%).

- **Second “open-label” phase:**

Sixty children were switched to the open-label add-on therapy according to the protocol, as follows:

- 30 patients <2 years were switched to concomitant therapy with timolol gel-forming solution 0.25% daily and dorzolamide 2% t.i.d.;
- and 30 patients ≥2 years were switched to 2% dorzolamide/0.5% timolol fixed combination (i.e. Cosopt) b.i.d.

Nevertheless, since the results of this open label phase were pooled with the monotherapy phase, it was difficult to determine the precise additional IOP decrease when dorzolamide was used in adjunct to timolol.

Furthermore, 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 were provided.

Nevertheless, pooled results suggested an additional IOP decrease for patients switched to add-on therapy.

Overall, the efficacy results from the paediatric study suggest that the mean IOP decrease observed in the dorzolamide group was comparable to the mean decrease observed in the timolol group. These results appeared to be in the same range than the IOP decreases reported by Portellos and al. in paediatric patients (-27%).

In the specific context of the present paediatric assessment, the efficacy results were considered of value to complete the SPC but not sufficient to introduce an indication in section 4.1 in children, since major deficiencies were identified for this paediatric study (no primary efficacy end-point).

In summary, the following major study’s deficiencies were identified:

- The optimal paediatric dosage has not been established.
- The reference product (i.e. timolol) is not currently registered for a paediatric use in Europe, except on the Dutch market. Given that the physical aspect of timolol gel formulation can be easily discerned from the aqueous fluid formulation of Trusopt, the double blind was only theoretical in this study.
- Efficacy of Trusopt monotherapy to decrease paediatric IOP was only a secondary objective of the study.
- The 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, while a smaller percentage would have been more realistic.
- There were no standardized protocols regarding tonometry and general anaesthesia procedures. There were no predefined criteria for treatment failures.
- No statistical analysis according to the widely accepted limit of non-inferiority for the anti-glaucoma drugs (i.e. of 1.5 mm Hg) was provided. In addition, no exploitable efficacy results were available for the few patients switched to adjunctive therapy was provided.
- Long-term efficacy data (> 12 weeks) were not available.

Summary of safety data in paediatrics:

- **Safety assessment from the protocole N°100/125 study:**

The primary objective of this study was to document an acceptable safety profile for dorzolamide in patients from 1 week to <2 years of age and in patients ≥ 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 was available regarding the choice of this wide limit of discontinuation. Results showed that:

- Three patients from the age cohort < 2 years, one in the dorzolamide group (1.8%) and two in the timolol group (7.4%), discontinued for clinical adverse events;
- Four patients from the age cohort ≥ 2 years and < 6 years, two in the dorzolamide group (3.0%) and two in the timolol group (5.7%), discontinued for clinical adverse experience.

In both age cohorts, a higher percentage of patients in the timolol group discontinued due to adverse events, but there were no significant differences between groups.

The observed proportion of patients who discontinued study therapy due to a drug-related adverse experience was 1.79% (n=1, 95% CI [0.05%, 9.55%]) in patients <2 years of age and 3.03% (n=2, 95% CI [0.37%, 10.52%]) in patients ≥ 2 years but <6 years of age.

No safety concerns were considered from this trial in the paediatric patients.

Overall, the most common adverse events reported were in the body systems of digestive, respiratory, and special senses.

Mainly, the safety profile of dorzolamide in paediatric patients reflected that seen in adults, except for digestive and respiratory disorder. Local side effects were the most common drug-related adverse events in adults and children. In older children (≥ 2 years but <6 years), the most common ocular adverse experience was ocular burning/stinging, while ocular injection was the most common in younger children (<2 years of age).

Overall, this study did not reveal any additional safety concerns in children: approximately 26% of paediatric patients experienced drug related adverse effects, the majority of which were local, non serious ocular effects such as ocular burning and stinging, injection and eye pain. A small percentage, < 4%, had corneal oedema or haze. Consequently, the Applicant has committed to submit narratives and follow-up information regarding the corneal edema/haze in the next PSURs. Local reactions appeared similar in frequency to comparator.

As dorzolamide is a topical carbonic anhydrase inhibitor for the treatment of elevated intraocular pressure, in order to explore the known adverse events “acid-base disturbances”, the chemistry laboratory test total CO₂ was performed at study day 1 and week 12. Only 1 patient <2 years who was initially randomized to dorzolamide 2% had a drug related laboratory adverse experience of CO₂ decreased, but this case was not clinically significant.

According to the paediatric study condition, the primary objective to demonstrate an acceptable safety profile was strictly reached. Nevertheless, it was concluded that the occurrence of uncommon adverse events might not be ruled out, in particular the risk of acid-base disturbances in relation with the pharmacodynamic profile of dorzolamide.

- **Post-marketing safety data:**

The Merck WAES database was searched for spontaneous reports from health care providers of adverse events with dorzolamide hydrochloride in patients <18 years from the time of product launch (international birth date 11-Nov-1994) through 31-May-2005.

A total of 27 reports, including 8 serious reports, were identified.

The most frequent adverse events were eye disorders, nervous system disorders, investigations, and skin and subcutaneous tissue disorders. Among the 4 serious adverse events reported in the nervous system disorder, 2 were in combination with brimonidine.

Three cases of metabolic acidosis in the very young infants, particularly with renal immaturity/impairment were reported, among which one was in association with acetazolamide that is not recommended with dorzolamide (SPC, Section 4.4):

1. In a child of 4-week old, who concomitant treatment was brimonidine, a convulsion and metabolic acidosis was reported. The dechallenge was negative for metabolic acidosis. There was not enough information to assess this case.
2. A 5-day-old child, with bilateral Peter's anomaly and renal immaturity developed metabolic acidosis, 7 days after starting dorzolamide. Dorzolamide was discontinued and the metabolic acidosis resolved the day after. This case was plausible, especially in patients with renal immaturity.
3. A 5-day-old male with multiple medical problems was prescribed dorzolamide with acetazolamide, latanoprost, and betaxolol. He developed a respiratory acidosis. Dorzolamide was discontinued and metabolic acidosis persisted. The effect was probably related to acetazolamide.

A signal of metabolic acidosis was reported in post-marketing data. The association dorzolamide / acetazolamide is not recommended in the SPC. A warning related to the use in paediatrics of less than 36 weeks gestational age or less than 1 week of age and in patients with significant renal immaturity was included in the section 4.4 of the SPC.

5. OVERALL DISCUSSION , BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

In Europe, the safety and effectiveness of Trusopt 2% had not been established in the paediatric population, although the drug was often used 'off-label'.

Trusopt 2% was primarily registered under the ex-Concertation procedure, amended through a Mutual Recognition Procedure and finally listed under the “EU worksharing project assessment of paediatric data of existing products”.

According to this procedure, the Applicant submitted a paediatric study primarily designed, as requested by FDA, for safety assessment. Amendments were proposed by the Applicant, in particular to introduce a paediatric use in the SPC of Trusopt 2% eye drops, solution in section 4.1 as follows: “In the short-term treatment of paediatric glaucomas as adjunctive therapy to betablockers and for monotherapy when other treatments have proved ineffective or are unsuitable.”

During the course of the procedure, the principle of a paediatric indication was first supported by the Co-Rapporteur, and 3 Member States. This recommendation was not endorsed by the Rapporteur and the majority of the other Member States. These countries considered the paediatric data submitted not sufficiently robust to introduce a full indication for children in Section 4.1.

Although the results of the single comparative study suggested a significant efficacy in decreasing IOP, there were several major objections for such a paediatric indication,

Further to the Rapporteurs and CMS questions, answers from the Applicant were provided. Most of the responses were considered acceptable, and the Applicant proposed to delete the formal paediatric indication, as previously claimed.

The new proposal was agreed by the Rapporteurs and CMS: a consensus was finally reached to introduce a short description of the paediatric study results in section 5.1 of the SPC.

In order to better present the paediatric data, additional changes to sections 4.2, 4.3, 4.4 and 4.8 were discussed. A consensus was found between members to introduce relevant statements with regard to the paediatric use in section 4.2, 4.4, and 4.8.