

**Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as
amended**

INN: Timolol

AT/W/0005/pdWS/001

Rapporteur:	AT
Finalisation procedure (day 120):	05.06.2011
Date of finalisation of PAR	01.08.2011

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VI
INN (or common name) of the active substance(s):	Timolol
MAH (s):	See section VI
Pharmaco-therapeutic group (ATC Code):	S01ED01
Pharmaceutical form(s) and strength(s):	Eye drops, Eye drops, solution

I. EXECUTIVE SUMMARY

Art. 45 of Reg. 1901/2006

By January, the 26th 2008, any paediatric studies already completed, by the date of entry into force, in respect of products authorised in the Community shall be submitted by the marketing authorisation holder for assessment to the competent authority.

The competent authority may update the Summary of Product Characteristics and Package Leaflet, and may vary the marketing authorisation accordingly. Competent authorities shall exchange information regarding the studies submitted and, as appropriate, their implications for any marketing authorisations concerned.

The EMA shall coordinate the exchange of information.

As requested by the EMA in a letter dated 14th October 2009 and in accordance with Article 45 of Regulation EC No 1901/2006 as amended, the Marketing Authorization Holders submitted 50 Studies / Publications. Only those concerning the treatment of children with Timolol maleate were considered for assessment.

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. Betaadrenoceptor 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 betablockers, 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.

Following topical administration, Timolol 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. Timolol reduces intraocular pressure without the common side effects of miotics such as night blindness, accommodative spasm and pupillary constriction.

SmPC and PL changes are proposed in sections 4.2, 4.4, 5.1, 5.2 and 2, 3.

II. RECOMMENDATION¹

After evaluating the presented data we conclude that the administration of Timolol maleate in children in Europe can only be recommended for a transitional period, while a decision is made on a surgical approach and in case of failed surgery while awaiting further options.

¹ The recommendation from section V can be copied in this section.

The submitted data is insufficient to demonstrate the efficacy and safety of the drug for its long term use in children. Another important issue to be considered is that many of the Timolol eye drop solutions available on the market contain Benzalkonium Chloride (BAC) as a preservative. It is known that BAC has a sensitizing effect and therefore leads to hypersensitivity on the one hand and may cause eye irritation on the other hand. So additionally to possible systemic side effects of Timolol that might occur due to resorption through the nasolacrimal duct, the effect of BAC has to be taken into account in this very sensitive patient group.

In this assessment report only the eye drop formulations are covered and no gelan formulation, since according to the line listing provided, only eye drop solutions should have been submitted. Furthermore due to difficulties in the application of the proper / accurate dose, gelan formulations are not recommended for use in the paediatric population.

Proposed SPC changes

Section 4.2 Posology and method of administration

Paediatric Population:

Due to limited data, Timolol could only be recommended for use in Primary congenital and primary juvenile glaucoma for a transitional period while decision is made on a surgical approach and in case of failed surgery while awaiting further options.

Posology:

Clinicians should strongly evaluate the risks and benefits when considering medical therapy with Timolol in paediatric patients. A detailed paediatric history and examination to determine the presence of systemic abnormalities should precede the use of Timolol.

No specific dosage recommendation can be given as there is only limited clinical data (see also section 5.1).

However, if benefit outweighs the risk, it is recommended to use the lowest active agent concentration available once daily. If IOP could not be sufficiently controlled, a careful up titration to a maximum of two drops daily per affected eye has to be considered. If applied twice daily, an interval of 12 hours should be preferred.

Furthermore the patients, especially neonates, should be strongly observed after the first dose for one to two hours in the office and closely monitored for ocular and systemic side effects until surgery is performed.

With regard to paediatric use, the 0,1% active agent concentration might already be sufficient.

Method of administration:

To limit potential adverse effects only one drop should be instilled per dosing time.

Systemic absorption of topically administered β -blockers can be reduced by nasolacrimal occlusion and by keeping the eyes closed as long as possible (e.g. for 3 - 5 minutes) after instillation of drops.

See also section 4.4, 5.2.

Duration of treatment:

For a transient treatment in the paediatric population (see also section 4.2 "Paediatric Population").

Section 4.4

Paediatric Population:

Timolol solutions should generally be used cautiously in young glaucoma patients (see also section 5.2).

It is important to notify the parents of potential side effects so they can immediately discontinue the drug therapy. Signs to look for are for example coughing and wheezing.

Because of the possibility of apnoea and Cheyne-Stokes breathing, the drug should be used with extreme caution in neonates, infants and younger children. A portable apnoea monitor may also be helpful for neonates on Timolol.

Section 5.1

Paediatric Population:

There is only very limited data available on the use of Timolol (0,25%, 0,5% twice daily one drop) in the paediatric population for a treatment period up to 12 weeks. One small, double blinded, randomized, published clinical study conducted on 105 children (n=71 on Timolol) aged 12 days – 5 years shows to some extent evidence, that Timolol in the indication *primary congenital and primary juvenile glaucoma* is effective in short term treatment.

Section 5.2

Paediatric Population:

As already confirmed by adult data, 80% of each eye drop passes through the nasolacrimal system where it may be rapidly absorbed into the systemic circulation via the nasal mucosa, conjunctiva, nasolacrimal duct, oropharynx and gut, or the skin from tear overflow.

Due to the fact that the blood volume in children is smaller than that in adults, a higher circulation concentration has to be taken into account. In addition, neonates have immature metabolic enzyme pathways and it may result in an increase in elimination half-life and potentiating adverse events.

Limited data show that plasma timolol levels in children after 0.25% greatly exceed those in adults after 0.5%, especially in infants and are presumed to increase the risk of side effects such as bronchospasm and bradycardia.

Proposed PIL changes:

Section 2 “Take special care with /...../”

Paediatric population:

Timolol eye drop solution should generally be used with caution in young patients. In newborns, infants and younger children Timolol should be used with extreme caution. If coughing, wheezing, abnormal breathing or abnormal pauses in breathing (apnoea) occur, the use of the medication should be stopped immediately. Contact your doctor as soon as possible. A portable apnoea monitor may also be helpful.

/...../ has been studied in infants and children aged 12 days to 5 years, who have raised pressure in the eye(s) or have been diagnosed with glaucoma. For more information, talk to your doctor.

Section 3

Posology:

Paediatric population:

A detailed medical examination should precede the use of Timolol. Your doctor will carefully evaluate the risks and benefits when considering treatment with Timolol. If the benefits outweigh the risks, it is recommended to use the lowest active agent concentration available once daily.

With regard to “the use in children”, the 0,1% active agent concentration may be sufficient to control pressure within the eye. If the pressure is not sufficiently controlled with this dosage, a twice daily application at 12-hourly intervals may be necessary. Patients, especially newborn, should be closely observed for one to two hours after the first dose and careful monitoring for adverse events should be carried out until surgery is performed.

Method of administration (Illustration through pictograms is recommended):

One drop only of Timolol should be instilled per dosing time.

After instillation keep the eyes closed for as long as possible (e.g. 3 – 5 minutes) and apply pressure to the corner of the eye closest to the nose to prevent Timolol eye drops spreading throughout the body.

Duration of treatment:

For a transient treatment in the paediatric population.

III. INTRODUCTION

Several MAHs submitted 11 published paediatric studies/reports for Timolol maleate, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

Short critical expert overviews have been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Timolol maleate and that there is no consequential regulatory action (Ursapharm).

In addition, the following documentation has been included as per the procedural guidance:

- A line listing
- An annex including SPC wording of sections 4.1 and 4.2 related to the paediatric use of the medicinal product (Alcon Labs).

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

Timolol maleate 0,1% 0,25% and 0,5% gel Formulation and eye drops
Betaxolol hydrochloride ophthalmic suspension 0,25%

It is not stated by the applicants, whether a specific paediatric formulation exists or not.

IV.2 Non-clinical aspects

1. Introduction

No non-clinical studies were submitted.

2. Non clinical study(ies)

None

3. Discussion on non clinical aspects

Assessor's comment:

Not applicable

IV.3 Clinical aspects

1. Introduction

The MAH Alconlabs submitted 3 published studies/reports for:

- 1) Betaxolol hydrochloride ophthalmic suspension 0.25% and timolol gel-forming solution 0.25% and 0.5% in pediatric glaucoma: A randomized clinical trial
David A. Plager DA, Whitson JT, Netland PA, Vijaya L, Sathyan P, Sood D, Krirshnadas SR, Robin AL, Gross RD, Scheib SA, Scott H, Dickerson JE,
Journal of AAPOS. Vol 13 (4) / August 2009
- 2) Influence of adrenergic antagonists on tear secretion in children
Samochowiec – Donocik E, Koraszewska – Mathuszezwska B .
Polish Journal of Pharmacology, 2004, 56, 871 – 873
- 3) Myopia progression in young school children. A prospective study of myopia progression and the effect of a trial with bifocal lenses and beta blocker eye drops
Jensen H
Acta Ophthalmol Suppl 1991; (200): 1-79

The MAH Alconlabs submitted 8 literature references = publications for:

- 1) Advances in the management of paediatric glaucoma
M Papadopoulos and PT Khaw
Eye (2007) 21, 1319-1325
- 2) Pharmacologic Management of Glaucoma in Childhood
Will Moore and Ken K Nischal.
Pediatric Drugs 2007; 9 (2): 71-79

- 3) Medical Therapy of Pediatric Glaucoma and Glaucoma in Pregnancy
Maris PJG, Mandal AK, Netland PA
Ophthalmology Clinics of North America, 18 (2005), 461 – 468
- 4) Timolol and pediatric glaucomas
McMahon CD, Hetherington J Jr, Hoskins I-ID Jr, Shaffer RN
Ophthalmology, 1981 Mar, 88(3):249-52.
- 5) Timolol in uncontrolled childhood glaucomas
Boger WP, Walton DS
Ophthalmology, 1981 Mar, 88(3):253-8
- 6) Clinical Experience with Timolol in Childhood Glaucoma
Hoskins HD Jr, Hetherington J Jr, Magee SD, Naykhin R, Migliazzo CV
Arch Ophthalmol, August 1985, Vol 103: 1163-1165
- 7) Plasma Timolol in Glaucoma Patients
Passo MS, Palmer EA, Van Buskirk EM
Ophthalmology, November 1984, Vol 91(11): 1361-1363

The MAH Ursapharm submitted 1 literature references = publication for:

- 1) Conservative treatment of the infantile glaucoma with Timolol, D-Epiphrine and Isoglaucan
Follmann P., Wix K, Kenyeres A.
Folia Ophthalmol. 15 (1990): 167 – 171

2. Published Clinical studies

A) published clinical Studies

- 1) Betaxolol hydrochloride ophthalmic suspension 0.25% and timolol gel-forming solution 0.25% and 0.5% in pediatric glaucoma: A randomized clinical trial

*David A. Plager DA, Whitson JT, Netland PA, Vijaya L, Sathyan P, Sood D, Krirshnadas SR, Robin AL, Gross RD, Scheib SA, Scott H, Dickerson JE
Journal of AAPOS Vol 13 (4) / August 2009*

➤ **Methods**

- Objective(s)
To describe the safety profile and clinical response on elevated intraocular pressure (IOP) of betaxolol hydrochloride ophthalmic suspension 0.25% (betaxolol) and timolol maleate ophthalmic gel-forming solution (TGFS) (0.25% and 0.5%), in subjects under 6 years of age.
- Study design
Randomised, double-blinded study

- Study population/Sample size
105 children (34 were randomized to betaxolol, 35 to TGFS 0.25%, 36 to TGFS 0.5%), aged 12 days to 5 years.
- Treatments
All received a “morning” and an “evening” bottle of medication. Parents were instructed to instil a single drop in each study eye from the morning bottle at 8 AM (30 minutes) and dose 1 drop in each study eye from the evening bottle at 8 PM (30 minutes).
- Statistical Methods
The primary efficacy parameter was an assessment of mean IOP change from baseline at 9 AM. Study visits were planned at weeks 2, 6, and 12. The primary analytic method consisted of describing the IOP data with means and 2-sided 95% confidence intervals. Repeated measures analysis of variance (ANOVA) was used to estimate the means and confidence intervals. Descriptive statistics were calculated for IOP, IOP change from baseline, and IOP percentage change from baseline.
The statistical significance of response to treatment was assessed by comparing the baseline IOP with the week 12 IOP using t-tests for paired comparisons (1-tailed test used for those subjects on no prestudy therapy) with a significance level of 0.05.

➤ Results

- Recruitment/ Number analysed
One hundred seven subjects were enrolled in the study and received study medication. Of these, 2 each in the betaxolol 0.25% and TGFS 0.25% treatment groups) were discontinued from the study prior to collection of any on-therapy study visit data; therefore, 105 subjects were evaluable for and included in the ITT analysis. Of the 107 enrolled, 15 subjects (5 on betaxolol, 7 on TGFS 0.25%, and 3 on TGFS 0.5%), including the 2 noted above, discontinued the study prematurely. The most common reason for subject discontinuation was inadequate control of IOP (2 in the betaxolol 0.25% group, 5 in the TGFS 0.25% group, and 3 in the TGFS 0.5% group).

Table 1. Subject demographics by treatment group

	Total		Betaxolol 0.25%		TGFS 0.25%		TGFS 0.5%		p-value*
	N	%	N	%	N	%	N	%	
Total	105	100.0	34	100.0	35	100.0	36	100.0	
Age									
1 week to <1 year old	17	16.2	6	17.6	6	17.1	5	13.9	0.9989
1 year to <2 years old	20	19.0	6	17.6	7	20.0	7	19.4	
2 years to <4 years old	32	30.5	11	32.4	10	28.6	11	30.6	
4 years to <6 years old	36	34.3	11	32.4	12	34.3	13	36.1	
Sex									
Male	61	58.1	17	50.0	26	74.3	18	50.0	0.0592
Female	44	41.9	17	50.0	9	25.7	18	50.0	
Race									
Asian	47	44.8	15	44.1	16	45.7	16	44.4	0.9075
Black or African American	15	14.3	4	11.8	4	11.4	7	19.4	
Caucasian	36	34.3	12	35.3	13	37.1	11	30.6	
Multi-racial	1	1.0	0	0.0	0	0.0	1	2.8	
Other	6	5.7	3	8.8	2	5.7	1	2.8	
Iris color									
Blue	14	13.3	5	14.7	6	17.1	3	8.3	0.6790
Brown	77	73.3	25	73.5	25	71.4	27	75.0	
Green	1	1.0	0	0.0	1	2.9	0	0.0	
Gray	2	1.9	1	2.9	1	2.9	0	0.0	
Hazel	8	7.6	3	8.8	1	2.9	4	11.1	
No iris [†]	3	2.9	0	0.0	1	2.9	2	5.6	
Diagnosis									
Primary congenital glaucoma	61	58.1	16	47.1	25	71.4	20	55.6	0.1241
Primary glaucoma associated with systemic or ocular abnormalities	16	15.2	4	11.8	5	14.3	7	19.4	
Glaucoma secondary to aphakia	28	26.7	14	41.1	5	14.3	9	25.0	

*p-value from χ^2 or Fisher exact test.[†]Patients with aniridia.

- Baseline data

For betaxolol 0.25%, mean IOP decrease from baseline was 2.3 mm Hg ($p = 0.008$); for TGFS 0.25% the reduction was 2.9 mm Hg ($p = 0.012$), and for TGFS 0.5% the reduction was 3.7 mm Hg ($p = 0.002$).

Because the study allowed enrolment of subjects either on or not on an IOP-lowering medication at the time of randomization, the change in IOP from baseline in these 2 subpopulations was analysed.

Table 3. Baseline IOP (mmHg) comparison

	N	Baseline average*
		Mean \pm SD
All patients		
Betaxolol 0.25%	34	24.6 \pm 5.5
TGFS 0.25%	35	23.2 \pm 5.5
TGFS 0.5%	36	24.4 \pm 5.7
Prior IOP-lowering therapy		
Betaxolol 0.25%	20	23.7 \pm 5.8
TGFS 0.25%	22	21.5 \pm 5.2
TGFS 0.5%	28	23.8 \pm 5.6
No prior therapy		
Betaxolol 0.25%	14	26.1 \pm 4.8
TGFS 0.25%	13	26.2 \pm 4.8
TGFS 0.5%	8	26.4 \pm 6.1

SD, standard deviation.

*Baseline average = average of the screening and baseline.

- Efficacy results
Fifty-nine percent of the betaxolol 0.25% subjects, 63% of the TGFS 0.25% subjects, and 78% of the TGFS 0.5% subjects were being treated with 1 or more IOP-lowering medications at the study start (Tables 3 and Fig 1). These subjects discontinued their prestudy therapy or therapies at the time of enrolment, crossing over to the masked, monotherapy study drug. All 3 treatments demonstrated a reduction in mean IOP. For subjects not on an IOP-lowering medication at the time of randomization, betaxolol 0.25%, TGFS 0.25%, and TGFS 0.5% produced statistically significant and clinically relevant mean reductions in IOP; When a 15% reduction from baseline IOP is used as a threshold to define responders to therapy, 38.2% of the betaxolol group, 45.7% of the TGFS 0.25% group, and 47.2% of the TGFS 0.5% group could be classified as responders.

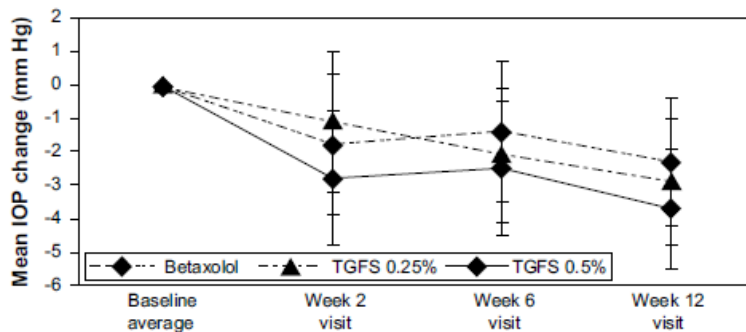


FIG 1. Mean IOP change from baseline (mm Hg) and 95% confidence intervals.

- Safety results
The evaluation of safety was based on all subjects (N = 107) who were enrolled into the study and received at least 1 dose of study medication. Adverse events in the overall safety population were predominately nonserious and generally mild to moderate in intensity. Of these, 7 were associated with cardiovascular parameters and not unexpected in patients exposed to beta-blockers.

Assessor's comment:

There are a number of limitations to this study. These include the relatively small number of subjects when compared to adult studies, the short duration of treatment (12 weeks), and the variability in the study population.

Another aspect is that the study has been performed with Timolol Gel formulation. Physicochemical properties of a gel formulation and eye drop solution can not be compared. However efficacy was demonstrated for Timolol and Betaxolol.

2) Influence of adrenergic antagonists on tear secretion in children

*Samochowicz – Donocik E, Koraszewska – Mathuszevska B
Polish Journal of Pharmacology, 2004, 56, 871 - 873*

➤ **Methods**

- **Objective(s)**
The aim of the study was to compare the results of tear film volume, conjunctival and corneal state of children eyes both treated with β -blocker and healthy ones.
- **Study design**
Not sufficiently described: Control group (healthy ones) and glaucoma patients
- **Study population /Sample size**
40 eyes of 20 children at the age from 7 to 17 years were examined. Group I (mean age was 14,6 years) – 20 glaucomatous eyes treated with 0.5% timolol twice daily during at least 12 months. Group II (mean age was 9,3 years) – 20 eyes of control age-matched group, who did not show any ophthalmological or general diseases that could affect the tear secretion.
- **Treatments**
Among study population there were 20 eyes of patients with juvenile and congenital glaucoma, that were treated with 0.5% timolol (containing BAC) twice a day for at least 12 months.
- **Outcomes/endpoints**
The patients were interviewed on their possible subjective disorder. The general and topical application of β -blockers can lead to alterations in aqueous part of a tear film, which was evaluated by Schirmer test. Schirmer I test without anesthesia and lissamine green staining was performed to evaluate conjunctival and corneal surface.
- **Statistical Methods**
The results were statistically analyzed by means of U Mann-Whitney and Fisher tests, $\alpha = 0.05$.

➤ **Results**

- **Baseline Data**
The results of Schirmer I test were from 14–31 mean, 27.8 ± 2.48 mm before treatment in group I and 16–35, mean 29.3 ± 2.67 mm in group II, $p = 0.16$.
- **Efficacy results**
After treatment with β -blocker the values of Schirmer I test were 12–24, mean 17.06 ± 1.78 mm.
The results of Schirmer I test were from 14–31 mean, 27.8 ± 2.48 mm before treatment in group I and 16–35, mean 29.3 ± 2.67 mm in group II, $p = 0.16$. After treatment with β -blocker the values of Schirmer I test were 12–24, mean 17.06 ± 1.78 mm.
Figure 1 shows that tear secretion was statistically significantly lower in eyes treated with topical β -blocker than in the control eyes, $p = 0.000004$.

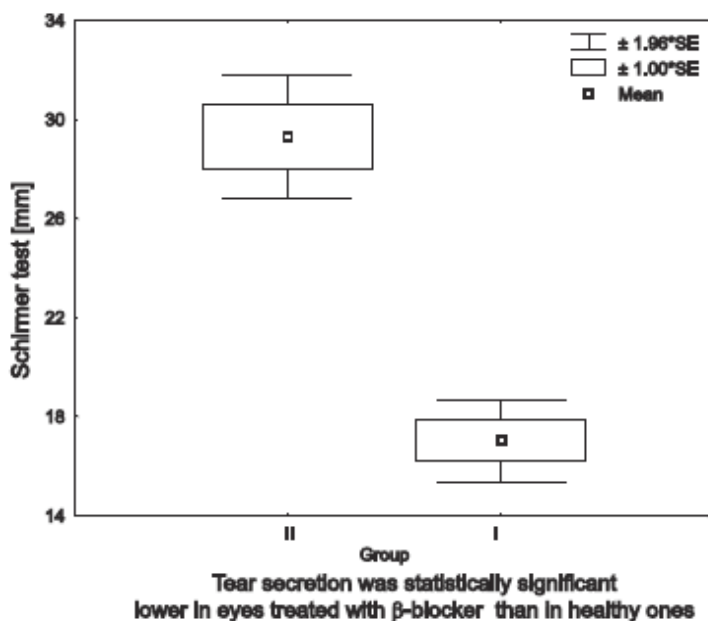


Fig. 1. Schirmer I test results in the eyes treated with β -blocker (Group I) and in the healthy children eyes (Group II)

In the group I keratoepitheliopathy was noticed in 4 (20%) treated eyes. In the group II, only single staining points were noticed (1st degree) in 2 eyes (10%).

The incidence of punctate corneal erosions was more frequent in the Timolol group than in healthy patients, but not statistically significant, $p = 0.37$.

There were no patients claiming any indisposition even among those with the 3rd or 6th degree of corneal and conjunctival changes Schirmer I test shows the significant decreasing of tear secretion in patients treated with timolol comparing to healthy children, $p = 0.000004$. The lowest result of Schirmer I test was 12 mm noticed in the group treated with β -blocker.

- **Safety results**

The patients from both groups I and II did not claim any subjective complaints. In both groups, the blinking caused the covering of a whole cornea.

Assessor's comment:

The study population is very small. Moreover this study evaluates the influence of Timolol on the tear secretion and does not go into further detail concerning the IOP lowering effect, safety or efficacy of Timolol in the claimed indication (glaucoma).

Nonetheless, statistically the tear secretion was significantly lower in eyes treated with topical β -blocker than in the control eyes, but it can not clearly be drawn whether the effect is related to Timolol itself or to the preservative BAC.

3) Myopia progression in young school children. A prospective study of myopia progression and the effect of a trial with bifocal lenses and beta blocker eye drops

Jensen H
Acta Ophthalmol Suppl 1991; (200): 1-79

The study population size was 159 (87 boys and 72 girls). The age ranged from 7 years 7 months to 13 years 6 months.

Assessor's comment:

The main focus of this publication lies on myopia. The influence of single vision lenses alone (control group), bifocal lenses alone and single vision lenses in combination with IOP lowering eye drops (Timolol) (timolol group) on the progression of Myopia was discussed.

The only information regarding timolol that can be obtained from this publication is the following:

In the timolol group a significant fall in pressure of about 3 mm Hg was found during treatment (2 years) with timolol maleate (1 drop 0,25% timolol twice daily). The baseline mean value was 16.5 mm Hg and the lowest mean IOP was 13.3 mm Hg after 6 and 18 months. After 2 years the treatment was discontinued. An additional examination was carried out one year after cessation of the trial in order to determine the progression after discontinuation of the pressure reducing eye drops. At that time, the mean pressure increased (15.00 mm Hg) after treatment was discontinued, although not to the previous level. The children with the highest IOP at baseline showed the largest drop in pressure, while those with initial pressures of up to 13 mm Hg showed no change – Table 8.1. During treatment with timolol maleate the pressure was significantly lower than that in the control group with single vision lenses (Mann Whitney rank sum test), but not at the follow-up examination one year after withdrawal of the drug.

Timolol group: Compared to the baseline IOP in the control group a statistically significant fall was found after 6 months, 18 months and 3 years.

Children in the timolol group with a high baseline IOP had a progression rate not statistically significant from the children in the control group. In contrast, the progression rate differed statistically in those with a low baseline IOP. After the third year there was no difference between the controls and timolol.

Assessor's comment:

This publication does not provide any information regarding safety or the pharmacological properties of Timolol in regard to its use as an eye drop solution in relation to Myopia.

Efficacy could be demonstrated since there was a statistically significant fall in comparison to the control group, but not after the follow up examination one year after withdrawal of the drug

It has to be pointed out, that the study population is regarded as not representative for the claimed indication of Timolol (No Glaucoma patients, but myopia patients). It remains questionable whether the results regarding the IOP lowering effect of Timolol in Myopia patients can be extrapolated to Glaucoma Patients.

B) Literature references = Publications

1) Advances in the management of paediatric glaucoma

*M. Papadopoulos and PT Khaw
Eye (2007) 21, 1319-1325*

Paediatric glaucoma can be classified into

- primary, where there is a developmental anomaly of the angle alone.

Primary congenital glaucoma (PCG) due to isolated trabeculodysgenesis is commonest.

- and secondary, where outflow obstruction is due to an ocular or systemic condition. Secondary, commonly caused by Axenfeld-Reiger Anomaly, Peters Anomaly, uveitis, aphakia, aniridia and Sturge – Weber syndrome

The goal of preserving a lifetime of vision for these children involves early, prompt control of IOP, correction of ametropia and rigorous amblyopia treatment, primarily surgical with medical therapy playing a supportive role, whereas in secondary glaucomas, medical therapy is first line except in congenital cases where surgery is often required to control IOP.

Medical Therapy:

Medical therapy often plays a supportive role. In PCG cases, preoperatively it may reduce IOP and allow the corneal oedema to clear and so improve visualisation of the angle at the time goniosurgery. Postoperatively, it can be used as an adjunct to maximise IOP lowering. In secondary glaucoma, it is often used as a first line therapy but in congenital or some infantile cases, surgery is often inevitable.

Plasma timolol levels in children after 0.25% greatly exceed those in adults after 0.5%, especially in infants and are presumed to increase the risk of side effects such as bronchospasm and bradycardia. In light of this, betaxolol (β_1 selective antagonist) and timolol gellan 0.25%, as an alternative because of less systemic absorption and the advantage of once a day dosing, have been widely prescribed in children. However, the recent introduction of timolol 0.1% has been useful in neonates and infants due to its superior risk profile. Blotting off excess drops and punctal occlusion and may also greatly reduce systemic absorption and should be taught to parents.

Topical carbonic anhydrase inhibitors are useful as second-line drugs, or when β -blockers are contraindicated. In a short randomised, controlled, double blinded, multicentre trial, dorzolamide was found to be well tolerated and effective for up to 3 months in children less than the age of 6 years. Similarly, topical dorzolamide was found to significantly reduce mean intraocular pressure from baseline. However, care must be taken with topical carbonic anhydrase inhibitors when corneal endothelial function is compromised. Possibility of longer, thicker, hyperpigmented eyelashes.

The use of systemic acetazolamide was limited because of a significant incidence of systemic side effects.

Assessors comments:

This report describes some treatment possibilities of paediatric glaucoma. Therefore no detailed information can be drawn on the IOP lowering effect of Timolol maleate, since there is no specific data dealing with Timolol concerning posology, safety and efficacy. However, due to the information provided, Timolol seems to be efficacious in the paediatric population.

Due to the superior risk profile the use of 0.1% Timolol eye drops solution is recommended in neonates and infants.

2) Pharmacologic Management of Glaucoma in Childhood

Will Moore and Ken K. Nischal.

Pediatric Drugs 2007; 9 (2): 71-79

An evidence-based review of the drugs available for the medical management of childhood glaucoma. Most topical drugs are safe. There are some significant exceptions, such as

brimonidine, which may cause apnea, among other life threatening adverse events, in infants. Drugs available are topical adrenoceptor antagonists, topical and systemic carbonic anhydrase inhibitors, prostaglandin analogs, adrenoceptor agonists, parasympathomimetics, and combination preparations.

Although many of the childhood glaucomas require surgery, many children require medical management either as long-term treatment or as temporizing measures before and for after surgical intervention.

Adrenoceptor Antagonists

are still not licensed for use in children. They act by reducing the rate of aqueous production and cause an effective reduction in IOP. The most commonly used include: timolol solution (0.25% and 0.5% twice daily [e.g. Timoptol] or gel-forming solution (Timoptol-LA or Timoptic XE) once per day or 0.1 % eye gel [Nyogel] administered at night); betaxolol (0.25% suspension and 0.5% solution twice daily, e.g. Betoptic); levobunolol (0.5% twice daily, e.g. Betagan); and carteolol (1% and 2% twice daily, e.g. Teoptics).

These agents are often used as first-line treatment.

Contraindications for β -blocker use include bradycardia, heart block, uncontrolled heart failure, asthma, and obstructive airway disease. These agents are best avoided in premature and small infants because they can cause breathing difficulties and bradycardia. If it is necessary to use a β -blocker then the authors prefer to use betaxolol (a β -selective drug), starting with the lowest dose (0.25%) and observing the patient after the first dose. Although betaxolol has a better systemic adverse effect profile than timolol, in adults, at least, it has an equally protective effect on the optic nerve.

Local adverse effects of β -blocker eye drops in children include ocular stinging, burning, pain, itching, erythema, dry eyes, allergic reactions including anaphylaxis and blepharoconjunctivitis, and, occasionally, corneal disorders.

Furthermore following treatment possibilities were discussed:

Carbonic Anhydrase Inhibitors:

Prostaglandin Analogs

Adrenoceptor Agonist

Parasympathomimetics

Combined Preparations

Discussion:

The mainstay of management for the congenital glaucoma is surgery. However most patients will undergo medical management of IOP pre- and/or post surgery. Care must be taken in applying topical ophthalmic medications to children. A newborn is estimated to require 50% of the adult dosage to obtain the same ocular concentration; this increases to 60% at 3 years and 90% at 6 years. However, 80% of each eyedrop passes through the nasolacrimal system where it may be rapidly absorbed into the systemic circulation via the nasal mucosa. Systemic absorption also occurs through the conjunctiva, nasolacrimal duct, oropharynx, gut, and the skin from tear over flow. This, combined with the fact that the majority of topical antiglaucoma medications are designed for adults and are only available in adult dosages should make the prescriber wary of adverse effects. The blood volume in children is smaller than that in adults, especially in neonates (5% that of adults). Therefore, absorbed drugs will have a higher circulating concentration. This combined with immature metabolic enzyme pathways (in neonates) may result in an increase in elimination half-life thus potentiating adverse effects.

To limit potential adverse effects only one drop of each topical medication should be administered per dosing time (parents may be tempted to give two or three drops at any one time to ensure adequate dosage). Occlusion of the nasolacrimal system with finger pressure over the medial canthus for 3 – 4 minutes is thought to reduce systemic absorption by as much as 40%. However, the practicalities of maintaining pressure over the medial canthus for 3 - 4

minutes for each eye, for every eye drop administered, would be beyond the abilities of most caregivers. Using or at least starting with the weakest dose available for each medication used would, therefore, make good clinical sense.

Using the minimum number of medications required to reach the desired effect should be the aim. To this end having a treatment plan is useful. When commencing a new medication, the clinician documents the desired effect (or limits of acceptability) for lowering the IOP; then, at follow-up, if this is not achieved, the medication can be stopped and an alternative tried, again with documentation of the desired effect. This may help to limit the number of medications used and therefore reduce the likelihood of ineffective Polypharmacy.

For a bottle of eyedrops to remain microbe free for 28 days a preservative is added. The most commonly used agent is benzalkonium chloride. Although very effective, it is also responsible for much of the discomfort experienced by patients receiving ophthalmic preparations. In vivo and in vitro studies have shown ocular surface inflammatory changes that are dose dependent and increase with the frequency of drop installation. The in vitro studies showed that benzalkonium chloride was, to a large part, responsible for these effects. This is a significant risk factor for the failure of filtering surgery for glaucoma. This, in addition to the fact that glaucoma is a chronic condition for which many years of treatment are expected, if not lifelong, is a further reason to use the minimum number of medications.

Another way to reduce the number of drops received per day is to use combined preparations, thereby minimizing the dosage of benzalkonium chloride and perhaps improving the ease of administration and or compliance with treatment. All combination preparations at present have timolol 0.5% as one of their constituents. Therefore, if changing from other β -blockers (e.g. betaxolol) to a combined preparation, observation for systemic adverse reactions would be prudent.

It is essential that the prescribing clinician is aware of potential adverse effects and how they may present, so that the child's carers can be warned of signs to look for. Perhaps the best example of this is coughing, rather than wheezing as in adults, once topical β -blockers are started.

Conclusion

In general, topical treatment is very well tolerated and systemic effects are uncommon. The notable exception is the potentially life-threatening effects of brimonidine in young and small infants.

Assessors comments:

This report gives a good overview of different treatment options in paediatric glaucoma. No detailed information can be drawn on the IOP lowering effect of Timolol maleate, since there is no specific data dealing with Timolol concerning posology, safety and efficacy. However, due to the information provided, Timolol seems to be efficacious in the paediatric population. The side effects in children were comparable to those in adults.

3) Medical Therapy of Paediatric Glaucoma and Glaucoma in Pregnancy

Maris JGP, Mandal AK, Netland PA
Ophthalmology Clinics of North America, 18 (2005), 461 – 468

Medical therapy is usually allocated to a supportive role in the management of paediatric glaucoma to reduce intraocular pressure temporarily or to clear the cornea so that surgical therapy, the definitive treatment for primary congenital glaucoma, can be undertaken.

Medical therapy of paediatric glaucoma:

When considering medical therapy in paediatric patients, clinicians should evaluate the risks and benefits of specific medications, use the minimum dosages required for therapeutic efficacy, and follow the patient closely for ocular and systemic side effects.

β - blockers

In 34 patients with childhood glaucoma, timolol was combined with other medical therapy, causing a definite improvement in 29%, a modest or equivocal improvement in 32%, and no improvement in 39%.

In 38 eyes being treated with timolol as adjunctive therapy, 37% of eyes were controlled at 22 mm Hg or lower.

In 89% of eyes with various types of pediatric glaucoma, lowering of intraocular pressure was achieved only in 20% of eyes.

Similarly, in 100 eyes with childhood glaucoma treated with timolol, 31% experienced a reduction of intraocular pressure.

After the initial response, however, increased intraocular pressure may occur over time.

Plasma timolol levels in children after treatment with 0.25% timolol greatly exceed those in adults after instillation of 0.5% timolol, particularly in infants. This is explained by the volume of distribution of the drug, which is much smaller in children. The ocular volume of the neonate is approximately half that of the adult, reaching full size by approximately 2 years, whereas the blood volume of the neonate as a function of body weight is only a small fraction of that of the adult. In addition, the infant's immature metabolic enzyme systems may prolong the half-life of drugs in the neonate from two to six times beyond that of the typical adult → increase the risk of systemic side effects.

In children older than 5 years of age, a reduction in resting pulse rate has been associated with Timolol. Side effects have occurred in 4% to 13% of children and timolol therapy has been discontinued in 3% to 7% of patients. Alarming side effects of timolol therapy, such as Cheyne-Stokes breathing and apnoeic spells, have been reported, especially in infants and younger children. Provocation of asthma has been associated with timolol treatment. Betaxolol, a selective β₁ antagonist, reduces the risk of pulmonary side effects in adults as compared with timolol, but its effect on children is not known.

Timolol in 0.25% and 0.5% solutions should be used cautiously in young glaucoma patients. Because of the possibility of apnea, the drug should be used with extreme caution in neonates. A detailed pediatric history and examination to elicit the presence of systemic abnormalities should precede the use of timolol. The use of 0.25% timolol instead of 0.5% timolol is strongly recommended to reduce the risk of side effects. Additionally punctal occlusion and simple eyelid closure after drop administration. Blotting off excess drops from the child's lids may help to minimize unwanted systemic absorption. Once-daily dosing with timolol 0.25% in a gelforming solution may similarly help to simplify the medical regimen.

Furthermore following treatment possibilities were discussed:

- *Carbonic Anhydrase Inhibitors:*
- *α₂ Agonists*
- *Other adrenergic agonists*
- *Cholinergic drugs*
- *Prostaglandin Analogs*
- *Osmotic drugs*

Summary:

The primary goals of medical therapy in paediatric glaucoma are to decrease intraocular pressure temporarily, to clear an oedematous cornea, and to facilitate surgical intervention. Before commencing medical glaucoma therapy in a child, clinicians need to consider the potential for side effects carefully. Paediatric population may be at increased risk of systemic

Timolol

AT/W/0005/pdWS/001

Page 18/36

side effects compared with adults as a result of their reduced body mass and blood volume for drug distribution.

Assessors comments:

This report gives a good overview of different treatment possibilities in paediatric glaucoma. No detailed information can be drawn on the IOP lowering effect of Timolol maleate, since this paper does not sufficiently go into detail concerning posology, safety and efficacy of Timolol. The use of 0.25% timolol instead of 0.5% timolol is strongly recommended in this report to reduce the risk of side effects. Due to the possibility of apnoea Timolol should be used with *extreme caution* in neonates.

4) Timolol and paediatric glaucomas

*McMahon CD, Hetherington J Jr, Hoskinsl-ID Jr, Shaffer RN
Ophthalmology, 1981, Mar, 88(3): 249-52*

➤ **Description**

Abstract: Thirty-eight eyes were treated by adding timolol to the medical regimen. After a suitable trial, attempts were made to reduce other glaucoma medications. Fifteen eyes with infantile glaucoma treated surgically at birth, experienced elevated intraocular pressure later in life. Another 15 eyes had glaucoma associated with congenital anomalies such as aniridia, Sturge-Weber syndrome, and mesodermal malformation. The group with infantile glaucoma demonstrated an average drop in pressure of 24% and 22% after one and three months, respectively. Six of the 15 eyes were controlled at 22 mm Hg or less. In the other group, intraocular pressure fell 30% after one month and 12% after three months. Five of the 15 eyes were controlled. Adverse effects occurred in five patients, timolol therapy was discontinued in two (7%). The IOP was not controlled in any of the eyes with timolol alone. [Key words: pediatric glaucoma, timolol] Ophthalmology 88:249-252, 1981

➤ **Methods**

- **Objective(s)**
The purpose of this paper was to report the initial findings of a study conducted on patients with various forms of childhood glaucoma.
- **Study design**
Not further described
- **Study population /Sample size**
38 eyes in 28 patients (ages between 6 months and 31 years). Group 1 consisted of 14 patients (21 eyes) with the diagnosis of primary infantile glaucoma (mean age 17 years). Surgery had been performed on each of these eyes. Elevated IOP developed later in life requiring medical therapy. Group 2 consisted of 14 patients (17 eyes) with glaucoma secondary to congenital anomalies (mean age 13 years). Most of these eyes had not been treated surgically prior to entry into this study.
- **Treatments**
Most of the patients were using some form of medical therapy to control the IOP at the time of entry into the study. Patients were instructed to instil one drop of timolol 0.25% into the involved eye every twelve hours *in addition to their other medications*. Follow up

examinations were done at one week, one month and three months. If the intraocular pressure was not controlled by the administration of timolol 0.25%, the strength was increased to 0.5%. When the IOP was controlled for a period of six weeks, attempts were made to reduce or discontinue the other medications.

➤ Results

- Efficacy results

Group 1: Three patients with bilateral infantile glaucoma (=6 eyes) were discontinued with timolol. The baseline IOP of the remaining 15 eyes was 34.00 mm Hg. The addition of timolol resulted in an 8 mm Hg (24%) decrease in the IOP at 1 month, and a 7.5 mm Hg (22%) decrease at 3 months. This reduction resulted in 6 of 15 eyes being controlled with an IOP of 22 mm Hg or less.

Group 2: Two patients (2 eyes) were discontinued timolol shortly after initiation of therapy due to adverse effects. The remaining 15 eyes had an average baseline IOP of 31.5 mm Hg. The addition of timolol resulted in a decrease of 9.5 mm Hg (30%) after 1 month, but only 4 mm Hg (12%) after 3 months. Five of the 15 eyes were controlled with pressures of 22 mm Hg or less.

The IOP was not controlled in any of the eyes with timolol alone.

- Safety results

Adverse side effects associated with the use of timolol were reported in 3 patients. These symptoms included asthmatic attack (1), bradycardia (1), dissociated behaviour (1) and light headedness (2). Two of the five patients discontinued timolol because of these effects. The first patient, 10 years old, experienced a severe asthmatic attack. A second patient was a 17 year old male whose pulse slowed from 72 to 48 beats per minute. Generally a high percentage was observed (17 out of 28) with moderate reduction in heart rate.

Assessors comments:

The specific influence of Timolol on the IOP lowering effect could not be determined clearly, because most of the study participants (24 from 28) were already on prestudy medication, which was attempted to be discontinued during Timolol therapy. None of the eyes could be controlled on Timolol alone. 7 of all patients were over 18 years of age and thus can not be considered for paediatric assessment.

Furthermore the small study population was heterogenic, because group 1 was treated after surgery (due to elevated IOP developed later in life and thus requiring medical therapy). Regarding group 2 it is stated that most of the eyes had not been treated surgically prior entering the study.

Further deficiencies:

- study design not described in detail
- limited sample size
- unknown randomization scheme
- unknown GCP conformity
- insufficient safety evaluation (see also safety results: which treatment concentration was applied, frequency of administration of the concomitant medication given)

5) Timolol in uncontrolled childhood glaucomas

Boger WP, Walton DS

Ophthalmology, 1981, Mar, 88(3): 253-8

➤ Description

Abstract: Thirty-four patients with childhood glaucoma who had difficult management problems in spite of conventional glaucoma medications were entered into an investigational protocol designed at a time when timolol was not available commercially. Since controlled studies in adult glaucoma had demonstrated the efficacy of timolol, a trial of the drug in these difficult childhood cases seemed justified. The study was approved by the Human Studies Committees of the Children's Hospital Medical Center and the Massachusetts Eye and Ear Infirmary, Boston, MA. These children have been followed for periods up to 2½ years. In general, timolol was added to the maximum tolerated medical therapy. Definite improvement was noted in 10 patients, modest or equivocal improvement in 11, and in 13 no substantial benefit to their course occurred when timolol was added. Youngsters over 5 years of age showed an average reduction in resting pulse rate of 6 beats/minute similar to that previously found in adult patients. Under 5 years of age no change in the resting pulse rate could be detected. One patient was discontinued from timolol for a possible adverse effect. The experience particularly in very young children is still quite limited, but the beneficial effects observed warrant further evaluation. [Key words: beta blocking agents, childhood glaucoma, timolol.] Ophthalmology 88:253-258, 1981

➤ Methods

- Objective(s)
The purpose of this report was to report the findings of a study conducted on patients with childhood glaucoma who had difficult management problems in spite of conventional glaucoma medications.
- Study design
Not further described
- Study population /Sample size
There were 34 patients (ages between 1 months and 38 years) with severe childhood glaucoma enrolled. Only 28 were below the age of 18 years.

Table 2. Causes of Childhood Glaucoma (34 patients)

Infantile glaucoma	
Prior to trabecular surgery	3
After trabecular surgery	10
Aniridia	3
Glaucoma secondary to	
Iridocyclitis associated with JRA*	4
Idiopathic iridocyclitis	2
Congenital rubella syndrome	8
Steroid-induced glaucoma	1
Miscellaneous	3

* Juvenile rheumatoid arthritis

- Treatments
Most of the Patients were instructed to instill one drop of timolol 0.25% or 0.5% into the involved eye every twelve hours *in addition to previously used glaucoma medications*. Intraocular pressures were checked at least once a week and more frequently in some patients during the early phase of treatment. If the response was satisfactory, re-

evaluation was performed 2 weeks, 6 weeks, and 12 weeks later, and then every 12 weeks. If pressure was not satisfactory one week after the addition of 0.25% timolol solution, the dosage was increased to 0.5%, one drop twice daily. Timolol was generally not used unless conventional medications or surgical procedures were insufficient or were contraindicated. Timolol was intended to be used over a period of 2.5 years.

➤ **Results**

- Efficacy results

Most of the cases were complex with multiple concurrent medications in addition to timolol.

Assessors comment:
There is no information whether the concurrent medication was up titrated or not. There is also a lack of information concerning the duration of treatment and the allocation either to one or both eyes.

A judgement was made whether timolol had been (+) a dramatic or definite intervention, or (±) a modest or equivocal intervention or (0) no clear benefit to the patient’s course (see table 3 below).

Assessors comment:
 There is no definition of the classification to the kind of intervention (“dramatic” or “definite” intervention, or a “modest” or “equivocal” intervention or “no clear benefit” to the patient’s course.

Table 3. Patient Response

	+ Definite Positive Intervention	± Modest or Equivocal Intervention	0 No Clear Benefit
Number of patients	9	12	13

Table 4. Timolol Response According to Age

	+ Definite Positive Intervention	± Modest or Equivocal Intervention	0 No Clear Benefit
Number of patients 0–9 years of age	1	4	6
Number of patients 10 years of age or older	9	7	7

Assessors comment:
 There seems to be a discrepancy between Table 3 and 4. Both tables show an absolute number of 34 patients enrolled in the study, but the number of study participants differ in the definite positive intervention (+) or modest to equivocal intervention (±) column. In table 3 and table 4 one study participant was classified as either + or ±.

The addition of timolol resulted in a dramatic or definite improvement in the IOP of 9 patients (Table 3). In 12 individuals, the result of adding timolol was only a modest or equivocal reduction in IOP. For 10 patients, it was quickly apparent that timolol was not contributing significantly to their management, and these patients went on to glaucoma surgery rather promptly. In 3 cases timolol helped initially, but they were again uncontrolled after several weeks or a few months and the patients went on surgery. Sometimes timolol helped in one eye but not in the other eye of the same child. For children over 5 years of age, the mean resting pulse rate was 79 beats/minute. After 2 weeks of timolol therapy, the mean resting pulse rate was 73 beats/minute. For the few children under 5 years, there was no detectable difference in the mean resting pulse rate before and during brief use of timolol therapy.

- **Safety results**

No adverse effects were noted after brief periods of administration of timolol in 3 infants (1 mo., 3 mo., 6 mo. of age). A possible adverse effect was noted in one young adult. After using timolol for 1 year to his left eye, inferior corneal epithelial opacification and generalized hypesthesia were noted.

The most regularly noted side effect was a slight and asymptomatic reduction in resting pulse rate.

➤ **Discussion**

Adding timolol to maximal therapy, which was done for most of these patients, is a different situation than starting timolol as the only glaucoma medication. If a patient is receiving no glaucoma medications and timolol is started, the intra ocular pressure decreases significantly, and then over the next few days there may be a gradual upward “escape” to a new pressure level. In this situation the IOP may escape, but it generally does not return to pretreatment levels. When added to maximal medical therapy, timolol again may produce a dramatic reduction in IOP. But as the pressure escapes over the next few days of therapy, some patients maintain substantial reduction in IOP, some escape substantially toward pretreatment levels, while some escape all the way back to pretreatment levels. Clinically significant “short-term escape” as well as “long-term drift” are more frequent and more marked when timolol is used in addition to maximal medical therapy in setting of severe glaucoma in comparison to the setting when timolol is the only glaucoma medication in early glaucoma.

It is striking that the population under 10 years of age did not respond to timolol therapy as well as the population over 10 years of age.

Experience with timolol in neonates and infants is quite limited.

Timolol is neither a cure for childhood glaucoma nor is it universally successful in lowering IOP on a long-term basis in severe glaucoma. Some of the pediatric patients who have had an initially favourable response to the addition of timolol have shown much less impressive improvement 6 months or 12 months later. There is still very limited information available concerning the safety of timolol in the paediatric population. Before timolol therapy is initiated in a child, it would be wise for the ophthalmologist to advise the parents, that it is the severity of the glaucoma and the possible complications of other therapeutic options, such as glaucoma surgery, that must be weighed against the unknown risks of side effects occurring in the future following prolonged usage of timolol.

Table 1. Timolol in Uncontrolled Childhood Glaucoma
Summary of Intraocular Pressure Readings

Patient No.	Diagnosis	Age	Glaucoma meds	IOP Pre-Timolol (mm Hg)	Eye Rx	IOP with Timolol Therapy Added											Summary			
						2 Wks	6 Wks	3 Mo	6 Mo	9 Mo	12 Mo	15 Mo	18 Mo	21 Mo						
1	CRS	24 yrs	E, P, C CAI	50 38	OD	34 33	cyclotherapy OD											±		
2	JRA	8 yrs	E, C, CAI	19 48	OS	14 40	filter OS											0		
3	CRS	18 yrs	E, C, CAI	23 35	OS	25* 8	23 22	24 17	24 7	25 9	23 6					+				
4	JRA	10 yrs	E, C, CAI	38 40	OD	32 34	35	trabeculodistals OD											0	
5	SO	17 yrs	C, CAI	18 47	OS	22* 28	16 27	16 29	trabeculectomy OS											±
6	CRS	13 yrs		31	OS	28†	26	27	27							±				
7	CRS	13 yrs	E, P, C, CAI	25	OD	19	20	25	27	16	14					+				
8	IB	11 yrs	P, CAI	32 24	OD	12 28‡	21 43*	14 29	22	36	trabeculectomy OD					=				
9	CRS	14 yrs	E, P (OS)	16 29	OS	17 25	trabeculectomy OS											0		
10	IG	12 yrs	P, C, CAI	25 21	OU	16 16	20 20	26 16	21 23	18 15	26 24	17 14	21 16			+				
11	IG	22 yrs	CAI	29	OS	22	22	18	19	18	24					±				
12	IG	38 yrs		22	OD	15	13	14	16	14	16	15					+			
13	IG	16 yrs	C, CAI	21 25	OU	18 16	19 19	22 25	20 26	17 20	17 18	15 25	23 25			±				
14	Misc	18 yrs	P, CAI	25 20	OU	18 15	17 16	18 14	17 15	21 16	21 16	18 13				=				
15	AN	14 yrs	C, CAI	21 37	OU	11 23	15 25	13 21‡	9 22	22 40	10	5	11	cyclotherapy OS		+ OD ± OS				
16	IG	10 yrs	CAI	24	OS	20	17	16	17	16	16	17					+			
17	Misc	4 yrs	CAI	30	OD	16	26	25	20							±				
18	IG	9 yrs	CAI	40 with C 40 with C	OU	45 no C 43 no C	40 no C 35 no C	cyclotherapy OD trabeculectomy OS											0	
19	IG	13 yrs	CAI	25 27	OS	26 24	22 18	20 25	—	25 18‡	25	cyclotherapy OS				0				
20	IG	2 yrs	CAI	24 with E 35 with E	OU	25 no E 28 no E	22 no E 30 no E	21 no E 27 no E	25 no E 29 no E	23 no E 29 no E	24 no E 36 no E					=				
21	CRS	13 yrs		40	OS	48	29	44‡	cyclotherapy OS											0
22	IG	1 mo		35 35	OU	31 32	(after 5 days of therapy and CAI)—goniectomy OU and CAI											0		
23	JRA	41 yrs	CAI	40	OD	30	20	23	33‡	31	16					+				
24	AN	9 yrs	E, C, CAI	48 37	OU	41 40‡	27 39	10 36	34 36	32 33	cyclotherapy OS					± OD 0 OS				
25	Misc	3 mo	CAI	50 40	OU	30 with P40 30	40	trabeculectomy left eye											0	
26	Misc	4 yrs	C, CAI	35 17	OD	21 18	16 18 15 16 14 12											+		
27	IG (w/ p goniectomy OU)	6 mo	CAI	36	OD	45	(3 days of therapy)—second goniectomy OU											0		
28	CRS	13 yrs	P, CAI	19 43 32	OU	30 35 30	cyclotherapy OU											0		
29	IG	10 yrs		24 34	OS	17 29	18 24	18 30	17 29	20 34					0					
30	CRS	14 yrs		8 31	OS	19 24	17 20	15 20	20 25							+				
31	JRA	15 yrs	E, CAI	38 9	OD	12 11	37 18	cyclotherapy OD											0	
32	IB	8 yrs	CAI	27 15	OD	28 14	32 18	41* 17	33 14	37 15	trabeculectomy OD					0				
33	IG	3 yrs		25 27	OS	20 22	14 18												=	
34	AN	13 yrs	C	19 27	OS	19 17	19 19												+	

Key: CRS = Congenital rubella syndrome; JRA = Iritis associated with juvenile rheumatoid arthritis; IB = Iridopteric uveitis; SO = Sympathetic ophthalmia; IG = Isthmic glaucoma; AN = Aniridia; Misc = Miscellaneous; E = Epinephrine; P = Pilocarpine; C = Cholinesterase inhibitor; CAI = Carbonic anhydrase inhibitor; * Timolol therapy was added to the fellow eye; † Pilocarpine 4% 1 drop qid added to left eye; ‡ EDCI performed OS; § Epiphora added; * Pilocarpine added to right eye

Assessors comment:

Besides table 1 no further information has been provided concerning the study population. Furthermore study design, randomization scheme and GCP conformity were not described satisfactorily. Moreover the patient sample size is limited (34 patients and the number of treated eyes not clearly defined).

Concerning the efficacy results the reference does not discuss the outcome in regard to adults and paediatric population separately. Safety results were only provided for four children. The remaining 24 children were not mentioned concerning the AE – neither relating quality nor quantity.

No clear information has been provided on how many patients timolol was used in, as a mono treatment or in addition to previously used medications. The duration of treatment (Timolol, concomitant therapy) is not discussed in detail.

Therefore no evaluable information regarding safety, efficacy and posology can be drawn from this publication.

6) Clinical Experience with Timolol in Childhood Glaucoma

*Hoskins HD Jr, Hetherington J Jr, Magee SD, Naykhin R, Migliazzo CV
Arch Ophthalmol, August 1985, Vol 103: 1163 - 1165*

➤ Description

● **We studied 67 patients (100 eyes) with childhood glaucoma who were treated with timolol maleate. Thirty of these patients (40 eyes) did not require additional surgery or medications after being treated with timolol (follow-up, from six to 60 months). Thirty-one eyes (78%) in this group had a pressure drop; 18 eyes (45%) had a pressure drop of greater than 10 mm Hg. We conclude that timolol is effective in the treatment of pediatric glaucoma, although there is a need to be aware of its potential complications.**
(Arch Ophthalmol 1985;103:1163-1165)

➤ Methods

- Objective(s)
The purpose of this report was to report the findings of a study conducted on patients with childhood glaucoma who were treated with timolol maleate.
- Study design
Not further described
- Study population /Sample size
The original study population of McMahon et al was resurveyed 4 years later to look for additional complications and to assess the long-term efficacy of timolol treatment in paediatric glaucoma. Additional patients who had started timolol treatment since the 1981 study were added after review of medical records from the files of Shaffer Associates Medical Group, San Francisco. Patients were included in the study if they started timolol therapy before their 18th birthday.

They studied 67 patients (100 eyes) who started topical timolol therapy before the age of 18 (table1). Fifty-five of these patients (87 eyes) had failed glaucoma surgery before beginning timolol therapy. The follow-up period ranged from 5 days to 5.5 years, with a mean length of 2.5 years.

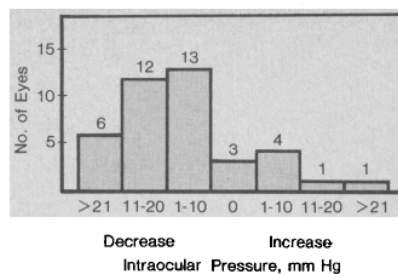
Source	Newborn- 1 mo	1-6 mo	6 mo- 1 yr	Years				
				1-4	5-8	9-12	13-17	18+
Present study	3	7	5	11	14	9	18	...
McMahon et al ¹⁰	...	2	1	0	6	3	8	8
Boger & Walton ⁸	1	1	1	4	2	7	12	6
Zimmerman et al ^{9*}	25	...	14	...	11

* Age groups for Zimmerman et al were 0 to 5 years, 5 to 10 years, and 10 to 30 years.

- Treatments
Not further described

➤ Results

- Efficacy results
Seventeen patients (31 eyes) required surgery due to inadequate reduction of IOP (Table 5). Of those, 15 patients (27 eyes) were restarted on timolol. In 8 patients (13 eyes), timolol therapy was discontinued because of successful surgery (4 eyes of 2 patients), noncompliance (2 eyes of 1 patient), complications (2 eyes of 2 patients), or lack of apparent effect (5 eyes of 3 patients). Fifty-nine patients (87 eyes) remained on timolol therapy at the end of the study. Fourteen of these 59 patients (20 eyes) not requiring glaucoma surgery after timolol therapy did require additional medications to control their IOP. The 30 patients (40 eyes) who had no eye surgery or additional medical therapy after initiating timolol were used to evaluate the efficacy of timolol in lowering IOP. Of these eyes, 78% had at least 1 mm Hg lowering of IOP; 58% had a pressure drop greater than 20%; 45% had a decrease in IOP in excess of 10 mm Hg. The average pretimolol IOP in these 40 eyes was 30.1 mm Hg (SD, 9.5) with final IOP of 22.7 mm Hg (SD, 8.5; $p < 0.001$).



Intraocular pressure response of 40 eyes receiving timolol therapy without additional surgery or medications.

Table 6 summarizes the effectiveness of timolol in lowering IOP in these 40 eyes as well as results reported by other authors.

Source	No. of Eyes	No. (%) of Eyes Showing Decrease
Present study*	40	31 (78)
McMahon et al ¹⁰	28	24 (86)
Boger & Walton ⁸	24	21 (88)
Zimmerman et al ⁹	13	13 (100)

*This number includes only patients using the same or less medications before timolol therapy.

- Safety results

Of the 67 patients, 7 experienced an adverse reaction to timolol. Only 2 of these patients were advised to stop the medication because of side effects.

A 10-year-old boy had a severe asthma attack immediately after starting timolol therapy, and a 17-year-old boy had a marked reduction in pulse rate. The remaining 5 patients suffered transitory reactions from timolol therapy. These included 2 cases in which the patient complained of dizziness, and 1 case each of asthma, drowsiness, and hyperactivity.

These and previously reported side effects from the studies of McMahon, Boger, Zimmerman, and their colleagues, are summarized in Table 4.

Side Effect	No. of Patients			
	Present Study	McMahon et al ¹⁰	Boger & Walton ⁸	Zimmerman et al ⁹
Asthmatic attack	2	1
Bradycardia	1	1	...	1
Disassociated behavior	2	1
Light-headedness	2	2	...	1
Corneal opacification	1	...
Tearing	1
Eye itching	2
Total Side Effects	7	5	1	5
Total No. in study	67	28	34	50

➤ Discussion

Twenty-eight of our 67 patients (43 of 100 eyes) used timolol for more than three years. They have not recognized any increase in side effects in these children after long-term use. Compliance with timolol therapy appears good. As far as they are aware, only one of the children failed to follow the prescribed timolol regimen. This high level of compliance is indicative of the generally well-tolerated nature of the drug. It is difficult to assess efficacy in the paediatric age group. Intraocular pressure measurements are often hard to obtain and, in very young children, must often be measured under general anaesthesia. Often these patients are receiving multiple medications and have undergone surgery. In the group who needed no further pressure lowering maneuver after starting timolol, there was a substantial mean IOP drop of 7 mm Hg. This is an encouraging result in these difficult glaucomas.

Although they cannot state on the basis of our study that 0.25% timolol is as effective as 0.5% timolol, the majority of patients who achieved stability with timolol did so with the 0.25% solution. More importantly, all of the patients with complications were using the 0.5% solution. The current strategy in children is to initiate therapy with the 0.25%

solution and increase to the 0.5% preparation only if the effect with the lower dosage is not adequate. One should then re-evaluate the IOP level to be sure that better control has been obtained with the stronger dosage.

The usual precautions of excluding patients with systemic contraindications and using the lowest effective dosage are particularly important in the use of this drug in childhood. It is also important to notify the parents of potential side effects so they can immediately discontinue the drug therapy.

Assessors comment:

The following important information is not further described:

- unspecified study design
- the strength given (0,25% or 0,5%)
- the number of eye drops given
- the frequency of instillation
- the frequency of measurement of IOP
- publication of Zimmerman TJ, Kooner KS, Morgan et al is missing "Safety and efficacy of timolol in paediatric glaucoma"
- 5 patients should have been included in the evaluation, because side effects or lack of efficacy are not accepted as reason for exclusion

Moreover following deficiencies are apparent: Data from McMahon, Boger and Zimmerman were pooled regardless the dosage regime, mono- or combination therapy. A discussion regarding the present study in relation to the cited literature references in detail is missing.

According to this literature reference 0,25% and 0,5% Timolol could be regarded as effective. However all side effects occurred under treatment with the 0,5% strength, while the majority achieved stability already with the 0,25% eye drop solution.

7) Plasma Timolol in Glaucoma Patients

*Passo, MS, Palmer EA, Van Buskirk EM
Ophthalmology, November 1984, Vol 91(11): 1361 - 1363*

➤ **Description**

Abstract: Plasma timolol levels were measured in our timolol-treated glaucoma patients employing three protocols: (1) measurements in ten patients over age 60 on chronic timolol therapy before, one hour, and three hours after receiving one drop of 0.5% timolol, (2) measurements in nine adult patients, with and without punctal occlusion, and (3) random measurement of plasma timolol in children on chronic timolol therapy while under general anesthesia. In the ten patients over age 60 years, baseline mean plasma timolol was 0.34 ng/ml, increasing to a mean of 1.34 ng/ml one hour after receiving drops. When punctal occlusion was applied, the mean one-hour plasma timolol diminished to 0.9 ng/ml, approximately 40% less than that observed without punctal occlusion. The plasma timolol levels examined in nine determinations in five children ranged from a low 3.5 ng/ml in a five-year-old child to 34 ng/ml in a three-week-old infant. [Key words: eyelid closure, pediatric, plasma levels, punctal occlusion, systemic absorption, timolol.] Ophthalmology 91:1361-1363, 1984

➤ Methods

- Objective(s)
A developed receptor-binding assay for timolol base allows quantitative analysis of systemic absorption of ocular timolol. Passo et al. used the assay to measure plasma timolol levels in patients on chronic timolol therapy.
- Study design
Not further described
- Study population /Sample size
Plasma timolol levels were measured in 5 young children (ages between three weeks to five years).
Random sampling from children receiving chronic timolol therapy for various forms of glaucoma was performed during general anaesthesia.
- Treatments
Four children received 0.25% timolol to both eyes, one 14-month-old child with unilateral glaucoma on 0.25% timolol to the left eye only.

➤ Results

- Efficacy results
The nine plasma timolol levels measured in 5 children ranged from 3.5 ng in a 5-year-old child to 34 ng per ml in a 3-week old infant.

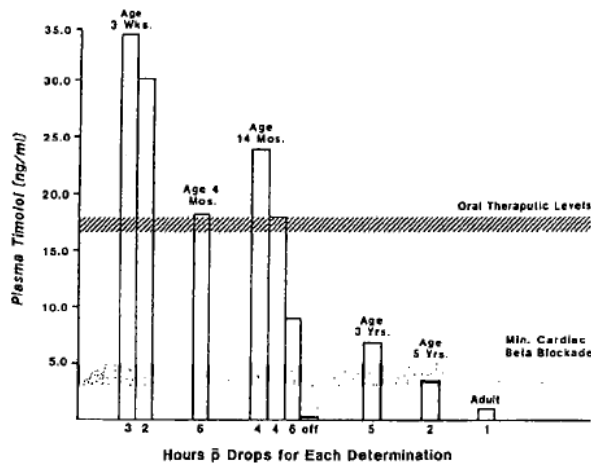


Fig 3. Histogram showing mean plasma timolol measured on nine separate occasions under general anesthesia in five children (ages 3 weeks–5 years) on timolol eye drops for glaucoma. The time elapsed from the drop instillation is noted below each bar. The mean one hour adult level from Figure 1 is included for comparison.

- Safety results
Only one of the five children experienced possible toxic side effects. The youngest experienced two apnoeic episodes while receiving timolol and a third episode several days after it was discontinued.

➤ **Discussion**

Measurable plasma timolol in all patients one hour after receiving timolol eye drops was observed.

Administering eye drops to small children in adult dosages results in very high blood levels. Considering that the ocular volume of the neonate is about half that of the adult, reaching full size by about age two years, while the blood volume of the neonate as a function of body weight is only a small fraction of the adult. Thus, administration of the usual adult ocular dosage may be needed for the eye, but, when systemically absorbed is diluted by a much smaller volume of blood.

Only one of the five children experienced possible toxic side effects. The youngest experienced two apnoeic episodes while receiving timolol and a third episode several days after it was discontinued. Apnea has been reported in other timolol-treated infants, but other factors could also have been contributors in all of these cases.

When timolol is used in small children, we recommend its administration in the lowest effective dose possible. It may be advisable to observe children for adverse effects for one to two hours in the office after drop instillation before describing to them for outpatient usage, for a history of asthma may not be available. A portable apnoea monitor may also be helpful for neonates on timolol.

Assessors comment:

Deficiencies of this study concerning the paediatric population:

- the study population size of 5 children
- the plasma timolol level is not listed separately for each study participant
- the number of eye drops given
- the frequency of instillation
- the frequency of blood sample collection

The main focus in this study was not the paediatric population. There is only a limited number of children (n=5; 3 weeks to 5 years). From these sparse data it can be concluded that the usual adult ocular dosage may be needed for the eye, but when systemically absorbed is diluted by a much smaller volume of blood, resulting in a possible increase of systemic side effects.

Furthermore it remains unclear whether the mentioned developed receptor-binding assay is validated or not.

8) Conservative treatment of the infantile glaucoma with Timolol, D-Epiphrine and Isoglaucan

*Follmann P, Wix K, Kenyeres A
Folia Ophtalmol 15 (1990): 167 - 171*

➤ **Description**

It is reported on the conservative therapy of the glaucoma in 57 children with medicaments not frequently used (timolol, D-epifrine, isoglaucan eye droplets and acetacolamide tablets). According to the experience of the author the age of the children is no contraindication for the administration of timolol, D-epifrine or isoglaucan.

➤ Methods

- Objective(s)
The purpose of this literature was to compare the benefit of treatment possibilities in paediatric patients with childhood glaucoma, who were treated with timolol maleate, d-epinephrine, isoglaucan eye droplets and acetazolamide tablets.
- Study design
Not further described
- Study population /Sample size
Fifty-seven patients (110 eyes) were examined. Four children had a buphthalmus only at one eye. They diagnosed primary buphthalmus in 63 eyes, secondary buphthalmus in 5 eyes, primary childhood glaucoma in 14 eyes and secondary childhood glaucoma in 28 eyes.
- Treatments
Sixty-nine eyes were treated with timolol. The age reached from 1 month to 8 years (mean age range 93.5 months). The remaining patients were treated with either D-epinephrine, isoglaucan or acetazolamide per os.
Sixty-three eyes were treated with 0.25% timolol and 6 eyes were treated with 0.5% timolol.

Tabelle 3. Typ der Konservativen Behandlung

	Konzentration %	Anzahl der Augen	%	Jüngstes Lebensalter	Durchschnittl. Beobachtungszeit (Mo)
Timolol	0,25	63	63	1 Mo	24 (1–62)
	0,5	6		8 Jahre	
D-Epifrin	0,1	55	50	1 Mo	34 (1–96)
Isoglaucan	1/8	7	12	30 Mo	25 (1–60)
	1/4	6			
Azetazolamide per os (max. 15 mg/kg Körpergewicht/Tag)		Anzahl der Kinder		2 Mo	3 (1–72)
		11			

➤ Results regarding Timolol treatment

- Efficacy results
In 25 (36%) of the timolol treated eyes the IOP was down regulated by timolol alone. In 64 % (44 eyes) the conservative treatment was supplemented by another glaucoma therapy treatment (Philocarpin, D-Epifrin, Eppy, Tonogen).
- Safety results
No local or systemic adverse effects were noted.

Assessors comments:

No relevant information concerning the posology, safety and efficacy can be taken from this study.

Results should be given more detailed:

- number of eye drops given
- the frequency of instillation
- the frequency of measurement of the IOP
- time and reasons for initiating additional medication
- number of patients with / without surgery on Timolol therapy

Furthermore there is no distinction in the evaluation between patients with or without previous surgery.

It remains questionable if the information regarding the safety is reliable, as no local or systemic AE were observed up to 62 months of treatment.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

Although the information provided by the MAH is limited, the use of Timolol maleate in the paediatric population can only be supported for a transitional period while decision is made on surgical approach and in case of failed surgery while awaiting for further options. This is pointed out in section 4.2 of the SmPC.

The provided data does not justify a pediatric indication in Section 4.1 of the SmPC. Moreover the submitted data is insufficient to demonstrate the safety of the drug for its long term use in children. No specific dosage recommendations could be given due to the limited data provided.

However, since there is no established medical treatment concerning congenital and juvenile glaucoma and due to the widely off label use of Timolol maleate in this indication, it can be concluded that the benefit of IOP lowering outweighs the risk of possible irreversible damage of the optical nerve leading to visual disturbance and visual loss.

To reduce the risk as far as possible, several warning statements and precautions for use were taken into account in the proposed product information as seen in the recommendation below. For safety reasons the use of the lowest dosage available, preferably preservative free and as an eye drops solution is recommended.

Further research and studies would be needed to support an indication for long term use of Timolol in the paediatric population in section 4.1 of the SmPC.

➤ Recommendation

Based on the data submitted its worth to point out that the use of Timolol maleate in the paediatric population can only be recommended for a transitional period in the lowest effective dose, while a decision is made on a surgical approach and in case of failed surgery while awaiting for further options, strictly under close monitoring.

Due to the superior risk profile, the development of a 0,1% ophthalmic eye drops solution, preferably preservative – free, should be encouraged.

Another important issue to be considered is that many of the Timolol eye drops available on the market contain Benzalkonium Chloride (BAC) as a preservative. It is known that BAC has a

sensitizing effect and therefore leads to hypersensitivity on the one hand and may cause eye irritation on the other hand. So additionally to possible systemic side effects of Timolol that might occur due to resorption through the nasolacrimal duct, the effect of BAC has to be taken into account in this very sensitive patient group.

Therefore the use of preservative-free eye drop solutions should be recommended for use in the paediatric population.

Furthermore due to difficulties in the application of the proper / accurate dose, gelan formulations are not recommended for use in the paediatric population.

Based on the provided data, the SPC should be amended as follows:

Proposed SPC changes

Section 4.2 Posology and method of administration

Paediatric Population:

Due to limited data, Timolol could only be recommended for use in Primary congenital and primary juvenile glaucoma for a transitional period while decision is made on a surgical approach and in case of failed surgery while awaiting further options.

Posology:

Clinicians should strongly evaluate the risks and benefits when considering medical therapy with Timolol in paediatric patients. A detailed paediatric history and examination to determine the presence of systemic abnormalities should precede the use of Timolol.

No specific dosage recommendation can be given as there is only limited clinical data (see also section 5.1).

However, if benefit outweighs the risk, it is recommended to use the lowest active agent concentration available once daily. If IOP could not be sufficiently controlled, a careful up titration to a maximum of two drops daily per affected eye has to be considered. If applied twice daily, an interval of 12 hours should be preferred.

Furthermore the patients, especially neonates, should be strongly observed after the first dose for one to two hours in the office and closely monitored for ocular and systemic side effects until surgery is performed.

With regard to paediatric use, the 0,1% active agent concentration might already be sufficient.

Method of administration:

To limit potential adverse effects only one drop should be instilled per dosing time.

Systemic absorption of topically administered β -blockers can be reduced by nasolacrimal occlusion and by keeping the eyes closed as long as possible (e.g. for 3 - 5 minutes) after instillation of drops.

See also section 4.4, 5.2.

Duration of treatment:

For a transient treatment in the paediatric population (see also section 4.2 "Paediatric Population").

Section 4.4

Paediatric Population:

Timolol solutions should generally be used cautiously in young glaucoma patients (see also section 5.2).

It is important to notify the parents of potential side effects so they can immediately discontinue the drug therapy. Signs to look for are for example coughing and wheezing.

Because of the possibility of apnoea and Cheyne-Stokes breathing, the drug should be used with extreme caution in neonates, infants and younger children. A portable apnoea monitor may also be helpful for neonates on Timolol.

Section 5.1

Paediatric Population:

There is only very limited data available on the use of Timolol (0,25%, 0,5% twice daily one drop) in the paediatric population for a treatment period up to 12 weeks. One small, double blinded, randomized, published clinical study conducted on 105 children (n=71 on Timolol) aged 12 days – 5 years shows to some extent evidence, that Timolol in the indication *primary congenital and primary juvenile glaucoma* is effective in short term treatment.

Section 5.2

Paediatric Population:

As already confirmed by adult data, 80% of each eye drop passes through the nasolacrimal system where it may be rapidly absorbed into the systemic circulation via the nasal mucosa, conjunctiva, nasolacrimal duct, oropharynx and gut, or the skin from tear overflow.

Due to the fact that the blood volume in children is smaller than that in adults, a higher circulation concentration has to be taken into account. In addition, neonates have immature metabolic enzyme pathways and it may result in an increase in elimination half-life and potentiating adverse events.

Limited data show that plasma timolol levels in children after 0.25% greatly exceed those in adults after 0.5%, especially in infants and are presumed to increase the risk of side effects such as bronchospasm and bradycardia.

Proposed PIL changes:

Section 2 “Take special care with /...../”

Paediatric population:

Timolol eye drop solution should generally be used with caution in young patients. In newborns, infants and younger children Timolol should be used with extreme caution. If coughing, wheezing, abnormal breathing or abnormal pauses in breathing (apnoea) occur, the use of the medication should be stopped immediately. Contact your doctor as soon as possible. A portable apnoea monitor may also be helpful.

/...../ has been studied in infants and children aged 12 days to 5 years, who have raised pressure in the eye(s) or have been diagnosed with glaucoma. For more information, talk to your doctor.

Section 3

Posology:

Paediatric population:

A detailed medical examination should precede the use of Timolol. Your doctor will carefully evaluate the risks and benefits when considering treatment with Timolol. If the benefits outweigh the risks, it is recommended to use the lowest active agent concentration available once daily. With regard to “the use in children”, the 0, 1% active agent concentration may be sufficient to control pressure within the eye. If the pressure is not sufficiently controlled with this dosage, a twice daily application at 12-hourly intervals may be necessary. Patients, especially newborn,

should be closely observed for one to two hours after the first dose and careful monitoring for adverse events should be carried out until surgery is performed.

Method of administration (Illustration through pictograms is recommended):

One drop only of Timolol should be instilled per dosing time.

After instillation keep the eyes closed for as long as possible (e.g. 3 – 5 minutes) and apply pressure to the corner of the eye closest to the nose to prevent Timolol eye drops spreading throughout the body.

Duration of treatment:

For a transient treatment in the paediatric population.

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

MAH	Name of the medicinal product	Strength	Pharmaceutical form
ALCON	Timolol 2,5 mg/ml	5	Eye drops, solution
Alcon	ögondroppar, lösning TIMOLOL ALCON 0.50% eye-drops	5 ml 10 ml	eye drops
ALCON CUSÍ, S.A.	CUSIMOLOL 0.25%	0.25%	Eye Drops, 5 ml
ALCON CUSÍ, S.A.	CUSIMOLOL 0.50%	0.50%	Eye Drops, 5 ml
Alcon	CUSIMOLOL 0.25% - 5ml	2.5 mg/ml	eye drops, solution
Alcon	CUSIMOLOL 0.5% - 5ml	5 mg/ml	eye drops, solution
Alcon Pharma GmbH, Blankreutestrasse 1, 79108 Freiburg, Germany	Cusimolol® 0,25 %	3,42 mg/ml	Eye drops solution
Alcon Italy S.p.A.	Cusimolol	0,25%	Eye drops, solution
SA Alcon-Couvreur NV (for national products)	TIMOLOL FALCON 0,25%	3.4 mg/ml	Eye drops, solution
Alcon	Timolol Alcon, 5 ml	2.5 mg/ml	Eye drops, solution
Alcon	Timolol Alcon, 5 ml, 3x5 ml	5 mg/ml	Eye drops, solution
Alcon	Timolol Alcon, 5 ml, 3x5 ml	2.5 mg/ml	Eye drops, solution
Alcon	Timolol Alcon, 5 ml, 3x5 ml	5 mg/ml	Eye drops, solution
Alco Hungary Ltd	Cusimolol 0.5%*	5 mg/ml	eye drops
Alco Hungary Ltd	Cusimolol 0.25%*	2.5 mg/ml	eye drops
ALCON LABORATORIES UK LIMITED	Timolol	0.25% w/v	Eye Drops, Solution
ALCON LABORATORIES UK LIMITED	Timolol	0.5% w/v	Eye Drops, Solution
ALCON	Tim-Alcon, 5 ml	5 mg/ml	Eye drops, solution
SA Alcon-Couvreur NV (for national products)	TIMOLOL FALCON 0,25%	3.4 mg/ml	Eye drops, solution
ALCON LABORATORIES UK LIMITED	Timolol	0,25%	Eye Drops, solution
ALCON LABORATORIES UK LIMITED	Timolol	0,50%	Eye Drops, solution
URSAPHARM Arzneimittel GmbH	Timo-COMOD 0,25 % Augentropfen	3,42 mg/ml	eye drops, solution
URSAPHARM Arzneimittel GmbH	Timo-COMOD 0,5 % Augentropfen	6,84 mg/ml	eye drops, solution
Laboratoires URSAPHARM S.A.S.	TIMOCOMOD 0,25 %	3,42 mg/ml	eye drops, solution
Laboratoires URSAPHARM S.A.S.	TIMOCOMOD 0,5 %	6,84 mg/ml	eye drops, solution
URSAPHARM Benelux B.V.	Timo-POS 0,25 %	3,42 mg/ml	eye drops, solution
URSAPHARM Benelux B.V.	Timo-POS 0,5 %	6,84 mg/ml	eye drops, solution
URSAPHARM Arzneimittel GmbH	Timo-COMOD® 0,1 %	1,37 mg/ml	eye drops
URSAPHARM Arzneimittel GmbH	Timo-COMOD® 0,25 %	3,42 mg/ml	eye drops

URSAPHARM Arzneimittel GmbH	Timo-COMOD® 0,5 %	6,84 mg/ml	eye drops
URSAPHARM Arzneimittel GmbH	Timolol-POS® 0,1 %	1,37 mg/ml	eye drops
URSAPHARM Arzneimittel GmbH	Timolol-POS® 0,25 %	3,42 mg/ml	eye drops
URSAPHARM Arzneimittel GmbH	Timolol-POS® 0,5 %	6,84 mg/ml	eye drops
URSAPHARM Benelux B.V.	Timo-POS 0,25 %	3,42 mg/ml	eye drops, solution
URSAPHARM Benelux B.V.	Timo-POS 0,5 %	6,84 mg/ml	eye drops, solution
URSAPHARM Benelux B.V.	Timo-COMOD® 0,25 %	3,42 mg/ml	eye drops, solution
URSAPHARM Benelux B.V.	Timo-COMOD® 0,5 %	6,84 mg/ml	eye drops, solution
URSAPHARM spol s.r.o.	Timo-COMOD 0.25 %	3,42 mg/ml	eye drops, solution
URSAPHARM spol s.r.o.	Timo-COMOD 0.5 %	6,84 mg/ml	eye drops, solution
URSAPHARM Arzneimittel GmbH	Timolol-POS 0.5 %	6,84 mg/ml	eye drops, solution
URSAPHARM Arzneimittel GmbH	Timo-COMOD picături oftalmice, soluție, 0,5 %	6,84 mg/ml	eye drops, solution
URSAPHARM spol s.r.o.	TIMOLOL-POS 0,25 %	3,42 mg/ml	eye drops, solution
URSAPHARM spol s.r.o.	TIMOLOL-POS 0,5 %	6,84 mg/ml	eye drops, solution