15 October 2010
EMA/531707/2010
Patient Health Protection

Assessment report for Xalatan and associated names

International non-proprietary name: latanoprost

Procedure no: EMEA/H/A-29 PAE/1270

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of Abbreviations

AEs	Adverse event (s)
ANCOVA	Analysis of covariance
AUC_{last}	Area under concentration time to curve from 0 to time to last measurable concentration
BAK	benzalkonium chloride
CI	Confidence interval
CL/F	Apparent plasma clearance
C_{max}	The maximum (peak) observed drug concentration following drug administration
CRF	Case report form
CV	Coefficient of variation
EU	European Union
IOP	Intraocular pressure
ITT	Intent-to-treat
JOAG	Juvenile Open-angle Glaucoma
LLOQ	Lower limit of quantification
LOCF	Last Observation Carried Forward
LS	Least squares
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
min	Minutes
mmHg	Millimetres of mercury
N	Number
OAG	Open angle glaucoma
PBT	Persistence, Bioaccumulation and Toxicity
PCG	Primary congenital glaucoma
PDCO	Agency's Paediatric Committee
PEC	Predicted Environmental Concentration
PG	Prostaglandin
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
POAG	Primary open-angle glaucoma
PP	Per protocol
SAEs	Serious Adverse event (s)
SD	Standard deviation
SE	Standard error
$t_{1/2}$	Elimination half life
T_{last}	Time to last measurable concentration
T_{max}	Time to reach maximum (peak) concentration following drug administration
yrs	years

1. Background information on the procedure

1.1. Submission of the dossier

The Marketing Authorisation Holder (MAH) Pfizer Ltd submitted on 16 April 2010 an application for a new paediatric indication for Xalatan and associated names, in accordance with Article 29 of Regulation (EC) No 1901/2006 as amended.

The eligibility to the procedure was agreed upon by the EMA/CHMP on 24 September 2009.

The MAH applied for the following new therapeutic indication: Reduction of elevated intraocular pressure in paediatric patients with elevated intraocular pressure and paediatric glaucoma.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/220/2009 for the following condition(s):

- Reduction of elevated intraocular pressure in the treatment of paediatric glaucoma

on an agreed paediatric investigation plan (PIP).

The PIP is completed.

The PDCO issued an opinion on compliance.

Licensing status

Xalatan and associated names has been given a Marketing Authorisation in the following EU Member States: Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, United Kingdom, as well as in Iceland and Norway.

1.2. Steps taken for the assessment

- The Rapporteur and Co-Rapporteur were appointed by the CHMP on 17 December 2009, as follows:
  - Rapporteur: Ian Hudson
  - Co-Rapporteur: Philippe Lechat
- The application was received by the EMA on 16 April 2010;
- The procedure started on 20 April 2010;
- The Rapporteur's and the Co-Rapporteur Assessment Reports were circulated to all CHMP members on 10 May 2010;
- The updated Rapporteur overview Assessment Report was circulated to all CHMP members on 14 May 2010;
- During the 17 – 20 May 2010 plenary meeting, the CHMP agreed on the consolidated List of Questions to be sent to the MAH. An extension of the timetable was agreed. The final LoQ and the timetable were sent to the MAH on 20 May 2010.
- The MAH submitted the responses to the CHMP consolidated List of Questions on 17 June 2010.

- The (Co-)Rapporteur Joint Assessment Report on the MAH's responses to the List of Questions to was circulated to all CHMP members on 7 July 2010.
- The updated (Co-)Rapporteur Joint Assessment Report on the MAH's responses to the List of Questions to was circulated to all CHMP members on 16 July 2010.
- During the meeting on 22 July 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, considered the new therapeutic indication to be acceptable and agreed on the amendments to the relevant sections of the SmPC and PL and the conditions to be fulfilled by the Marketing Authorisation Holder.

2. Scientific discussion

2.1. Introduction

Problem statement
Paediatric glaucoma is a complex collection of diverse pathophysiological entities defined by the basic glaucoma pathophysiology of an abnormally elevated IOP (> 21 mmHg) which represents the primary risk factor for optic nerve damage and consequent visual field loss.

Paediatric glaucomas as classified by the European Glaucoma Society, include primary congenital glaucoma (PCG), primary infantile glaucoma, juvenile open-angle glaucoma (JOAG), and secondary glaucoma. Secondary glaucomas are either acquired or related to an underlying ocular abnormality such as aphakia, Sturge-Weber syndrome, uveitis, and trauma. The majority of paediatric glaucomas are diagnosed with either congenital or aphakic glaucoma (~70%).

In paediatric patients with PCG, surgery (e.g. trabeculotomy/goniotomy) is the first line gold standard treatment but pharmacological therapy can be used when needed as initial management until surgery and as maintenance treatment after surgery. Nevertheless, in non-PCG paediatric patients (e.g. aphakic glaucoma and JOAG) the initial treatment is usually pharmacological.

Regardless of the type of glaucoma, IOP reduction is the highest priority for halting or slowing disease progression in paediatric patients. Although ocular hypertension is not yet glaucoma, adolescents with ocular hypertension should be monitored closely and should be treated for potential progression to JOAG in case their risk is high enough.

Over the last 30 years, effective IOP-lowering agents have been introduced, including non-selective and selective beta-blocking agents, prostaglandin analogs, topical carbonic anhydrase inhibitors and alpha 2-agonists. Combinations of these medicines are frequently used as treatment to appropriately control IOP in children with glaucoma. Most of these medications are not yet approved for use in children.

Although not approved for use in the paediatric population, there have been publications on the use of latanoprost in paediatric glaucoma. Case reports and review articles suggest that latanoprost has IOP-lowering benefits in paediatric glaucoma patients, who ranged in age from 0.92 (11 months) to 19 years, primarily in non-PCG (mainly JOAG) patients, whereas, these reports suggest that patients with PCG tend to show little to no clinically relevant IOP-lowering response with pharmacological therapy.

About the product
Latanoprost is an ester analogue of prostaglandin F2α that reduces IOP by increasing uveoscleral outflow. Xalatan (latanoprost), 0.005% eye drops solution and associated names, has been approved in several EU Member States via national or mutual recognition procedure since 1996, for "reduction of elevated intraocular pressure in adult patients with open angle glaucoma and ocular hypertension". The recommended daily dose in adult is one eye drop (approximately 1.5 µg latanoprost) in the affected eye(s), with an optimal effect obtained if administered in the evening. In adult patients, a once daily drop of latanoprost 0.005% solution has shown to reduced diurnal IOP by 22 to 39% over 1 to 12 months' treatment in controlled clinical trials.

The Xalatan eye drops solution contains benzalkonium chloride 0.02% (BAK) as preservative.

The efficacy and safety of latanoprost in adults has been shown in several clinical studies since the initial marketing authorisation. This included three pivotal phase III trials (9200PG004, 9200PG005, 9200PG006) demonstrating that latanoprost (50 µg/ml) dosed once daily is at least as effective as timolol dosed twice daily in lowering IOP in adults with open angle glaucoma and ocular hypertension and two long-term (up to 5 years) follow up safety studies (9400PG034 and 9700PG071).

Approximately 42,942,000 patient-years have been exposed to latanoprost since the 4th quarter of 1996 until 3rd quarter of 2009.

The development programme in paediatric patients
Scientific advice on the paediatric development plan for latanoprost was provided and agreed by the CHMP in April 2007. In January 2008, the PDCO adopted a positive opinion on the PIP for latanoprost followed by subsequent modifications.

The following studies were agreed in the PIP:

1. Pharmacokinetic study (A6111139): a 2 week, open-label study to evaluate the systemic exposure of latanoprost acid in paediatric subjects administered the adult dose of latanoprost 1.5 µg/eye topically (1 drop of 0.005%) including a comparison to adult subjects.

2. Clinical study (A6111137): a 12-week study to evaluate the efficacy and safety of latanoprost (0.005% latanoprost once daily) compared with timolol (0.5%/0.25%) twice daily in paediatric subjects ≤18 years old with glaucoma in at least one eye.

3. Two long-term follow-up safety studies to be conducted post-approval:

Study A6111143, a prospective, non-interventional, longitudinal cohort study aiming primarily to evaluate the long-term (3 years) impact of treatment with Xalatan on ocular development, ocular neurodegenerative disease, hyperpigmentation changes in the eye, corneal endothelial function/corneal thickness, and ocular tolerability by comparing paediatric subjects treated with latanoprost (n=150) with those not treated with latanoprost or other prostaglandin analogues (n=50).

Study A6111144, a prospective enhanced surveillance programme to be initiated following completion of the A6111143 cohort study, to collect information on adverse events of special interest such as hyperpigmentation changes in the eye among paediatric patients treated with Xalatan over a 7-year period.

2.2. Non clinical aspects

Environmental risk assessment (ERA)
The ERA submitted in this application is in accordance with the current guidelines on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00).

No further PBT screening is required as log D value (log DpH 7.4) is 4.3. In Phase I, a worst case PEC in surface water is 7.5 x 10^{-9} mg/l (0.0000075µg/l). Therefore, Phase II environmental fate and effects analysis are not required.

2.3. Clinical aspects

In support of this application for a paediatric indication and in full compliance with the agreed PIP, the two pivotal studies – phase I pharmacokinetic study (study A6111139) and phase III clinical study (study A6111137) - were submitted and are hereafter discussed.

Clinical Pharmacology

Pharmacokinetics

Study A6111139

This was a single open-label study of the systemic pharmacokinetics of latanoprost acid in paediatric and adult subjects receiving treatment with latanoprost 0.005% for glaucoma or ocular hypertension for at least two weeks.

This study was conducted to evaluate the systemic exposure of latanoprost acid in paediatric subjects administered with the adult dose of latanoprost 1.5µg/eye topically (1 drop of 0.005%).

Population

A total of 47 subjects of either gender were enrolled: 22 adults (>18yrs) and 25 paediatric subjects (0 to<18yrs). The paediatric subjects were subdivided by age range - 0 to <3yrs, 3 to <12yrs and 12 to <18yrs - and included 8 subjects, 10 subjects and 7 subjects, respectively. Subjects were randomly assigned to receive the study treatment.

Patients with active ocular inflammation/infection or a history of ocular inflammation/infection within 3 months prior to screening, history of ocular trauma or surgery in either eye within 14 days of screening, and history of hypersensitivity to latanoprost, benzalkonium chloride, or any other ingredients contained in Xalatan were excluded from the study.

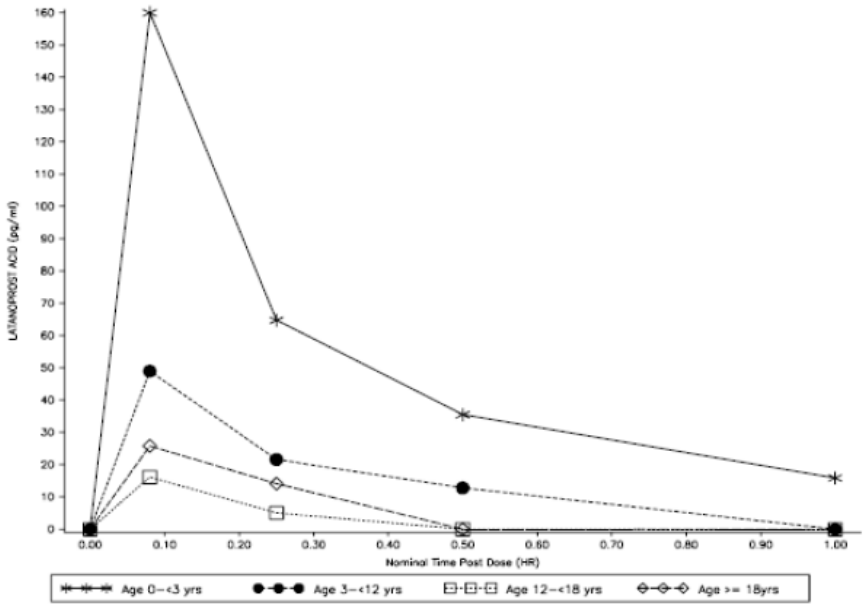
Pharmacokinetic and statistical methods

Descriptive statistics were computed for the pharmacokinetic parameters and concentration data. The 90% CI for the geometric means was computed for Cmax and AUC (last).

Results

None of the pre-dose samples contained detectable levels of latanoprost. The maximum (peak) concentrations following latanoprost administration (Cmax) was observed 5 minutes post-dose across all age groups. However, exposure was higher for the 0 to <3 yrs age group. The slop of the terminal elimination phase was similar across age groups. The overall results of study A6111139 are detailed below (Figure S1 and Table 1).

Figure S1. Latanoprost Acid Concentration-Time Plot (Median Values) Evaluable Pharmacokinetic Analysis Set



Summary calculations have been calculated by setting concentration values below the lower limit of quantification to zero.

Table 1. Summary of Pharmacokinetic Parameters

	Age Group			
	0 to <3 Years	**3 to <12 Years**	**12 to <18 Years**	**≥18 Years**
N[a]	**8**	**10**	**7**	**22**
C_{max} (pg/ml)				
N[b]	7	9	6	17
Mean	**140.4**	67.5	24.3	**29.2**
CV%	46	81	65	43
Median	166	49.0	16.2	25.8
Range	32.6-214	14.7-167	11.0-49.7	10.8-53.3
Geometric Mean (95% CI)	121 (81.1-181)	49.1 (34.5-69.9)	20.8 (13.5-32.0)	26.7 (20.7-34.5)
T_{max} (min)				
N[b]	7	9	6	17
Median	5.0	5.0	5.0	5.0
Range	5-15	5-5	5-5	4-18
T_{last} (min)				
N[b]	7	9	6	17
Median	60.0	30.0	10.0	20.0
Range	5-60	5-30	5-15	5-30
AUC_{last} (pg.min/ml)				
N[b]	7	9	6	17
Mean	3016	865	173	448
CV%	71	92	99	76
Median	2716	588	106	380
Range	81.5-6550	36.8-2220	27.5-420.0	27.0-1140
Geometric Mean (95% CI)	1830 (799-4195)	439 (211-911)	99.7 (40.7-244)	296 (174-504)
$t_{1/2}$ (min)				
N[b]	5	5	0[c]	4
Mean	20.1	12.0	-	20.5
CV%	24	29	-	35
Median	19.0	11.3	-	18.4
Range	14.9-28.0	9-17.3	-	14.3-30.8

Abbreviations: CV% = Coefficient of variation, CI = confidence interval, min = minimum, CSR = Clinical Study Report
[a]Total number of subjects in the treatment group; [b]Number of subjects contributing to the mean; [c]None of the subjects had sufficient data to characterise the terminal elimination phase.
Summary calculations have been calculated by setting concentration values below the lower limit of quantification to zero.

Latanoprost acid systemic exposure was higher in younger children (approximately 2-fold higher in the 3 to 12yrs age group and approximately 5-7 fold higher in the 0 to <3yrs age group) compared with adults. The short plasma elimination half-life of latanoprost acid (<20 min) was not extended in any age group.

The duration of systemic exposure assessed by the time to last measurable concentration (tmax) remained brief following once-daily dose administration. Plasma latanoprost acid concentrations were below the LLOQ of the assay by 60 minutes post-dose in all group ages but the 0 to 3yrs group.

The relationship between Cmax values and body weight as well as the inter subject variability appears to indicate that exposure to latanoprost acid trended with body weight. As body weight decreased plasma latanoprost acid concentrations tended to increase.

Discussion and Conclusion on pharmacokinetics

Results of study A6111139, comparing systemic exposure in paediatric subjects with adults, have shown that no accumulation is expected to occur in paediatric patients since all subjects received latanoprost for at least four days prior to pharmacokinetics investigation and no pre-dose measurable plasma level of latanoprost was observed. The study indicates that plasma elimination half life remains short (<20 minutes) and the same in all age groups.

Substantial differences in the systemic exposure in the younger patients between the 0 to <3yrs old group (5-7 fold higher) and 3 to <12yrs old group (2-fold higher) as compared to adults were seen. Although transient and probably explained by the lower body weight and volume of distribution, the higher systemic exposure observed particularly in the youngest patients was further discussed by the MAH at CHMP request. An estimation of the safety margin was performed for this group of patients.

The maximum tolerated dose (MTD) for the ocular route was estimated to be 11 µg/kg, approximately 275-fold higher than the approved ophthalmic dose. Consequently, the safety margin in adult patients

is approximately 275 as well. Taking into account the higher systemic exposure (5 to 7 fold higher) evidenced in children of less than 3 years old, the safety margin in this younger subgroup of patients was estimated to be 40 to 55 fold higher, approximately.

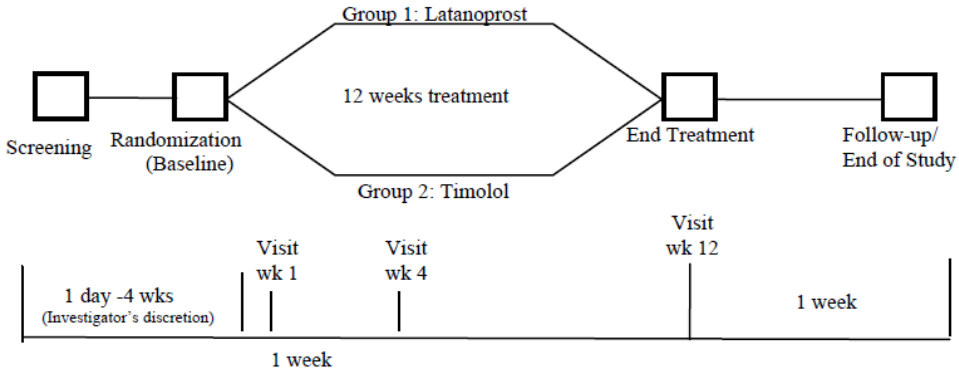
The higher exposure to latanoprost in the youngest age group is unlikely to have negative consequences on systemic tolerability to the treatment with latanoprost.

Clinical Efficacy

Study A6111137

This was a phase III, prospective, randomised, double-blind, 12-week, parallel group study assessing the efficacy and safety of once daily dose of latanoprost 0.005% versus timolol 0.5% administered twice daily (or 0.25% twice daily for subjects < 3 yrs old) in paediatric patients from birth to ≤ 18 yrs old with glaucoma in at least 1 eye (with neonates requiring to be at least 36 weeks gestational age).

Figure S1. Study Design



Abbreviation: Wk = Week

Objectives

The primary objective was to demonstrate non-inferiority of latanoprost to timolol within a margin of 3mmHg with an option of switching to superiority in the event that the lower limit of the 95% confidence interval for treatment effect lies not only above the non-inferiority margin but also above zero.

Secondary objectives included the evaluation of safety and the comparison of the proportion of subjects with at least a 15% lowering of baseline intraocular pressure (responder analysis) with latanoprost 0.005% (once daily) and with timolol 0.5% (optionally 0.25% for subjects younger than 3 yrs old, twice daily) in paediatric subjects <18 yrs of age with glaucoma.

Population

Male and female subjects from 36 weeks of gestational age to ≤ 18 yrs old with diagnosed paediatric glaucoma who were on topical therapy or naïve to pharmacological treatment and selected with a morning baseline visit IOP > 22mmHg in at least one eye.

Patients with prior cyclodestructive procedures or previous long-term therapeutic intervention with either timolol or a prostaglandin which failed to control elevated IOP or in whom no improvement was expected by pharmacologic treatment in addition to filtering surgeries or drainage implants, were excluded. Other exclusion criteria are standard with regards to assessment of ocular medicinal products.

Patients were randomised (1:1) into latanoprost or timolol treatment group. Randomisation was stratified by age group (0 to <3 yrs, 3- <12 yrs and 12-18 yrs), diagnosis (PCG, non-PCG) and IOP of the study eye (<27, 27 – 31, >31 mmHg) at baseline.

Treatments
Dosing with either latanoprost 0.005% or timolol 0.5% (or optionally 0.25% for subjects younger than 3 yrs old). Enrolment was staged by age categories (12-18 yrs, 3-<12 yrs; 0-<3 yrs) following results from the pharmacokinetic study (A6111139) in each corresponding age cohort.

No concomitant use of IOP lowering medication was authorised during the 12 weeks duration of the study except if after 1 week of treatment, IOP was uncontrolled (IOP ≥35 mmHg) therapy could be switched to open-label concomitant therapy (latanoprost 0.005% + timolol 0.5% or optionally 0.25%).

These subjects were still considered active study participants.

Results
Patient disposition
A total of 139 patients were randomised. Of which 137 received the study treatment (ITT population): 4 discontinued from the latanoprost group and 8 from timolol group (6 on the 0 to <3yrs group, 3 on the 3 to <12 yrs and 3 on the 12 to 18 yrs age group).

Major protocol violations were reported in 21 patients in the ITT population (11 and 10 in the latanoprost and timolol group, respectively). In addition more 9 patients were excluded: 3 for not having received study medication for more than 1 week (1 in the latanoprost group and 2 in the timolol group) and 6 who did not have week 1 IOP measurement (3 in the latanoprost group and 3 in the timolol group). The per protocol (PP) population, was defined as patients with no major protocol violations and who received at least 1 week of study medication and had at least week 1 IOP measurement during the 12 week treatment period.

The following table (table 2) presents the numbers of patients included in each analysis dataset.

Table 2 Data sets analysed

	Latanoprost n (%)	Timolol n (%)	Total n (%)
Assigned to study treatment	69	70	139
Number of subjects treated	68	69	137
Analyzed for Efficacy			
PP	53 (76.8)	54 (77.1)	107 (77.0)
ITT	68 (98.6)	69 (98.6)	137 (98.6)
Analyzed for Safety			
Adverse events	68 (98.6)	69 (98.6)	137 (98.6)

Demographic and baseline characteristics
In the ITT population the majority of patients were white with age ranging from 0.17 years (2 months) to 18 yrs. The 0 to < 3 yrs age group is noted to have a lower number of patients (17 in each treatment group) than the other age groups (3 to <12 yrs with 26 and 29 patients in the latanoprost and timolol groups, respectively and 12 to 18 yrs age group with 25 and 23 patients in the latanoprost and timolol groups, respectively).

The most common primary diagnosis was PCG with the higher prevalence seen in the children from 0 to < 3 yrs old (i.e. 82.4% in the latanoprost group and 70.6% in the timolol group). The prevalence of JOAG was higher in patients with 12 to 18 yrs old (48.0% in the latanoprost group and 52.2% in the timolol group). The overall prevalence of aphakic glaucoma was 11.8% in the latanoprost group and 10.1% in the timolol group and tended to be higher in subjects with 3 to 12 yrs old (15.4% in the latanoprost group and 13.8% in the timolol group). The study population is representative of the target population.

Prior treatments were mostly topical and included beta-blocking agents, prostaglandin analogs, topical carbonic anhydrase inhibitors and alpha 2-agonists and combinations with timolol. A total of 48 out of 68 patients (71%) in the latanoprost group and 38 out of 69 patients (55%) in the timolol group received prior ocular anti-hypertensive medications for glaucoma before the start of the study.

At baseline visit, subjects were to have discontinued any topical ocular anti-hypertensive medication for at least 24h before. The washout period duration were at the discretion of the investigators depending on the class of anti-glaucoma medication previously administered and according to the severity of the condition.

Efficacy results

Primary efficacy results

The results of the primary efficacy analysis for the PP population (using the ANCOVA model) shows that the lower limit of the 95% confidence interval is above the non-inferiority margin of -3mmHg, demonstrating the non-inferiority of latanoprost to timolol. Table 3 (below) summarises these results.

Table 3. ANCOVA model for IOP reduction (mmHg) at week 12 (LOCF), PP population

	Latanoprost N=53	Timolol N=54
Baseline		
Raw value		
Mean (SD)	27.3 (5.46)	27.8 (6.18)
Median (Range)	26.0 (22.0, 53.5)	25.8 (22.0, 46.0)
Week 12 (LOCF)		
Raw value		
Mean (SD)	20.2 (6.32)	21.9 (7.20)
Median (Range)	20.0 (10.0, 38.0)	20.3 (12.5, 52.0)
Reduction[a]		
Mean (SD)	7.1 (6.38)	5.8 (6.37)
Median (Range)	7.0 (-5.4, 32.0)	6.8 (-26.0, 20.0)
LS Mean (Standard Error)	7.18 (0.81)	5.72 (0.81)
Versus timolol		
LS Mean Difference	1.46	
95% CI LS Mean Difference	(-0.81, 3.74)	
p-value[b]	0.2056	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; IOP = intraocular pressure; LOCF = last observation carried forward; LS = least squares; mmHg = millimeters of mercury; N = number of subjects in population; PCG = primary congenital glaucoma; PP = per protocol; SD = standard deviation

a IOP reduction = baseline IOP minus postbaseline IOP

b P-value from an ANCOVA model with IOP reduction (baseline IOP minus postbaseline IOP) as the dependent variable, treatment (latanoprost vs timolol) and baseline diagnosis (PCG vs non-PCG) as factors and baseline IOP as a covariate.

Further analyses on the primary endpoint, including age as an additional factor and including the interaction terms, were consistent demonstrating non-inferiority of latanoprost compared to timolol.

The analysis of the primary endpoint using the ITT population also showed that the lower limit of the 95% confidence interval for the treatment difference was clearly above the non-inferiority margin although the estimated treatment difference was somewhat lower (-0.89 mmHg vs. -0.81 mmHg).

It is noted that, although the pre-defined non-inferiority margin was -3mmHg, the lower limit of the 95% confidence interval has been shown above -1.5mmHg in all primary efficacy analyses.

As recommended in *CPMP Points to Consider on Missing Data* (CPMP/EWP/1776/99), additional sensitivity analyses were performed using different methods of handling missing data other than the LOCF method. Results in the PP and ITT population using 3 additional sensitivity analyses also confirmed the non-inferiority of latanoprost over timolol for the reduction of IOP.

It is noted that the average reduction of 6-7 mmHg observed in the study population with either latanoprost or timolol is clinically relevant and the magnitude of the reduction consistent with previous results in adults and in paediatric studies.

Secondary efficacy results

Secondary analyses provide results in accordance with primary analysis. Mean IOP reductions from baseline range from 6.7 to 7.8 mmHg in the latanoprost group and from 5.3 to 6.9 mmHg in the timolol group. Mean IOP reductions in the latanoprost group were numerically slightly greater than in the timolol group at each study visit (weeks 1, 4, and 12) showing a tendency in favour of latanoprost efficacy in line with the tendency observed in adults.

The proportion of responders (≥15% reduction in IOP over the 12 week period) were all above 50%. Numeric trends in responder rate were in favour of latanoprost group in both PP population (60% *vs* 52%, for latanoprost and timolol, respectively) and ITT population (59% *vs* 57%, for latanoprost and timolol, respectively). This confirms that mean IOP decreases observed in both treatment groups are of clinical relevance. An additional responder analysis based on a target IOP of 18 mmHg by reference to

the Advanced Glaucoma Intervention Study (AGIS) was provided. The results with this more stringent criterion continue to numerically favour latanoprost over timolol as shown in table 4 (below).

Table 4. Proportion of subjects with IOP < 18 mmHg at both weeks 4 and 12

	PP Population				ITT Population			
	Latanoprost		Timolol		Latanoprost		Timolol	
	Total	Responder*	Total	Responder*	Total	Responder*	Total	Responder*
All	53	17 (32%)	54	9 (17%)	68	19 (28%)	69	12 (17%)
PCG	28	11 (39%)	26	5 (19%)	31	11 (35%)	31	6 (19%)
Non-PCG	25	6 (24%)	28	4 (14%)	37	8 (22%)	38	6 (16%)

Subgroup analysis for IOP reduction

PCG and non-PCG

The analysis of the primary endpoint for subgroups by diagnosis, PCG or non-PGC, indicated that for both subgroups the effect of latanoprost was non-inferior to that of timolol. The lower limit of the 95% confidence interval was above the non-inferiority margin for both subgroups although the estimated treatment difference was higher for the non-PCG subgroup than for those patients with PCG for the PP population. This was confirmed for the analysis of subgroups of the ITT population although the difference in effect between the subgroups was somewhat less than for the PP population.

The efficacy in PCG and non-PCG patients was further analysed by paediatric subgroup population. It is noted that similar to what is seen in the full population, also for PCG and non-PCG subpopulations an inconsistency of effect across the age ranges, is observed. Table 5 (below) shows the change from baseline at week 12 in IOP (mmHg), PP population.

Table 5: Change from baseline at week 12 in IOP (mmHg), PP population

		Latanoprost	Timolol	Latanoprost	Timolol	Latanoprost	Timolol
		Full population		PCG Subgroup		Non-PCG Subgroup	
0-<3 years	n	13	13	11	8	2	5
	Mean	5.5	2.0	6.1	4.7	2.3	-2.3
	LS mean	3.86	0.89	NA	NA	NA	NA
	Difference (95%CI)	2.98 (-3.69, 9.64)		1.45 (-4.08, 6.98)		4.55 (-22.87, 31.97)	
3-<12 years	n	20	24	11	13	9	11
	Mean	6.5	7.9	5.4	6.0	7.7	10.1
	LS mean	6.73	7.77	NA	NA	NA	NA
	Difference (95%CI)	-1.04 (-3.69, 1.61)		-0.62 (-4.46, 3.22)		-2.37 (-7.58, 2.84)	
12 – 18 years	n	20	17	6	5	14	12
	Mean	8.6	5.9	6.3	4.6	9.6	6.4
	LS mean	8.00	6.19	NA	NA	NA	NA
	Difference (95%CI)	1.81 (-1.42, 5.04)		1.73 (-6.97, 10.44)		3.22 (-1.53, 7.96)	

NA: Not Available

Overall, the PCG group reaches at least 15% IOP reduction from baseline which is considered relevant according to literature (e.g. Enyedi 2002). Better results are observed for non-PCG patients older then of 3 years of age reaching at least 20% IOP reduction from baseline while results from the non-PCG

younger strata are not interpretable due to the very low number of subjects (2 in the latanoprost group and 5 in the timolol group). Nevertheless, it is acknowledged that the subgroups by age for the PCG and non-PCG patients in general included a very low number of patients hence not allowing a reliable statistical comparison to be made.

Baseline IOP levels

The analysis of the primary endpoint for subgroups by baseline study IOP levels (<27, 27-31, and >31 mmHg) was provided at CHMP request. Most of the study subjects had baseline IOP values in the 22 to <27 mmHg range (57% in the latanoprost group and 59% in the timolol group) in the PP population. The imbalance of the number of patients in the two subgroups of higher pressure, did not allowed any conclusion on treatment differences. Nevertheless, differences in baseline IOP were adjusted for the analysis of the full population.

Wash-out period

The results were further analysed for washout period in relation to the pharmacological classes of prior topical ocular anti-hypertensive medication to rule out any potential influence of inadequate washout period. The standardised washout period of 28 days used in adult glaucoma studies was considered inappropriate for paediatric patients since such a period would expose subjects to an unacceptable risk of IOP and consequently susceptible to permanent eye damage.

A total of 33 out of 68 subjects (49%) in the latanoprost group and 29 out of 69 subjects (42%) in the timolol group did not meet the minimum washout duration requirements recommended in adult glaucoma studies. The primary efficacy results were reanalysed to include only patients who were either pharmacologically naïve or who had a washout period consistent with adult guidelines. In both ITT and PP analysis population, the results confirm the findings for all subjects showing a similar trend of clinically relevant decrease in IOP from baseline (approximately 6-7 mmHg) for latanoprost and timolol.

Age

Further analysis of the primary variable was conducted for subgroups by age for the PP population. The estimated treatment difference was in favour of latanoprost (but without statistical significance) for the youngest and oldest groups (2.98 and 1.81 mmHg respectively) but for the 3 to <12 yrs age group it was in favour of the timolol group (-1.04 mmHg). With regard to older strata (3 to <12 yrs and 12 to 18 yrs), results showed that mean decreases in IOP from baseline remained as expected for latanoprost (6.5 and 8.6 mmHg, respectively).

In the younger (0 to < 3 yrs old) subgroup that included a very low number of patients in each arm of treatment (i.e. 13 patients) the mean decrease in IOP observed with timolol was particularly low (i.e., 2 mm Hg, which can be considered clinically irrelevant). Latanoprost did numerically better than timolol and mean IOP decrease obtained with latanoprost remained in the accepted range of efficacy (5.5 mm Hg). The 95% confidence interval for the estimated difference in the 0 to <3 yrs age group was wider than in the older age groups due to high variability of IOP measurements in the youngest group. Results for the analysis of the ITT population (17 patients in each treatment group) were similar.

Although the number of patients included in this age group is very low, further analysis by dose of timolol received was carried out to help clarifying if a lower dose of latanoprost could be used in the 0 to < 3yrs old patients. Amongst the 17 subjects in the ITT population that were treated with timolol: 4 received the 0.25% dosing and all 4 were included in the PP population. Table 6 (below) shows the baseline characteristics and treatment response from the 13 subjects younger then 3 yrs in the PP population.

Table 6. Treatment and response in subjects younger than 3 yrs, timolol treatment group, PP population

Timolol Dosage	Baseline Diagnosis	Age (year)	Switched to Open-Label Therapy	IOP Reduction[a] at Week 12 (LOCF[b])
0.5%	Non-PCG	1.08	Yes	-26.0
	Non-PCG	2.42	No	3.0
	Non-PCG	2.75	No	2.0
	PCG	0.33	No	1.0
	PCG	0.42	No	7.0
	PCG	0.92	No	5.5
	PCG	1.33	No	4.0
	PCG	1.58	Yes	9.0
	PCG	2.08	No	7.5
0.25%	Non-PCG	0.83	Yes	5.0
	Non-PCG	1.33	Yes	4.5
	PCG	0.50	No	1.0
	PCG	1.08	Yes	2.5

[a] IOP reduction = baseline IOP – postbaseline IOP
[b] Last observation carried forward; excluding observations collected after switching to open-label concomitant therapy.

It is noted that 3 out of 4 subjects (75%) who initially received 0.25% timolol were switched to open-label therapy whereas only 2 out of 9 subjects (22%) who initially received 0.5% timolol. This may suggest that the 0.25% timolol dose might be insufficiently effective in lowering IOP in the 0 to <3 year age group.

The mean IOP reduction from baseline in the latanoprost <3 year age group reaches 20% which can be considered as clinically relevant according to the European Glaucoma Society Guideline, although this percentage remains lower than the percentages of IOP reduction observed in older age groups (i.e. 25% in 3 to <12; 31% in 12 to 18).

<u>In patients below 1 year and above 1 year of age</u>
To address the differences in the efficacy expected from developmental reasons especially below the age of 12 months as compared to adults, an analysis comparing the mean IOP change from baseline between subjects younger than 1 year and those older was performed. Table 7 (below) shows the results in the PP population.

Study Week	Summary Statistics	Younger than 1 Year		1 Year or Older	
		Latanoprost	Timolol	Latanoprost	Timolol
Week 1	N	4	5	49	49
	Mean (SD)	2.5 (9.75)	4.6 (5.94)	7.0 (4.24)	6.2 (7.75)
	Median (Range)	6.5 (-12, 9)	5.0 (-5, 10)	6.0 (-2, 22)	7.0 (-36, 21
Week 4	N	4	3	45	44
	Mean (SD)	1.3 (11.93)	3.0 (6.08)	7.5 (4.25)	5.5 (8.06)
	Median (Range)	3.0 (-14, 13)	6.0 (-4, 7)	7.0 (-5, 16)	6.9 (-26, 22
Week 12	N	4	4	42	39
	Mean (SD)	1.8 (12.20)	3.6 (3.09)	8.4 (5.32)	7.3 (4.44)
	Median (Range)	-4.0 (-5, 20)	3.3 (1, 7)	7.8 (1, 32)	7.0 (1, 20)

* Subjects who switched to protocol-specified open-label concomitant therapy were considered as active study participants; therefore, analyses excluding and including subjects on open-label therapy were conducted.

Since the majority of subjects younger than 1 year had PCG diagnosis (78% in PP and 85% in ITT), evaluation of subjects with a PCG diagnosis was performed. The number of latanoprost-treated subjects in the PCG subgroup was:

PP population: 28 subjects (3 subjects were younger than 1 year and 25 subjects were 1 year or older)

ITT population: 31 subjects (5 were younger than 1 year and 26 were 1 year or older)

In this PCG group mean (SD) IOP reductions at week 12 (LOCF) were for both age groups <1 year and ≥1 year, respectively:

→PP population: 4.0 (13.89) and 6.1 (4.76) mmHg,
→ITT population: 6.0 (11.04) and 6.0 (4.73) mmHg.

The fact that only 5 patients (ITT population) younger than 1 year old were exposed to latanoprost precludes any meaningful interpretation. It was noted that 2 of these 5 patients experienced an increase of IOP at 12 weeks whereas such increase occurred in 2 of the 26 patients above 1 year of age. This is considered not unexpected due to the majority of patients in the 0 to <3 yrs age group being diagnosed with PCG, for which the standard care is surgery and resistance to pharmacological therapy with either latanoprost or timolol to be expected particularly in surgical naïve patients.

Subgroup analysis of responders
The proportion of responders (percentage of patients with at least 15% IOP reduction from baseline) in subgroups was consistently numerically higher in the latanoprost groups compared to timolol group. As expected, a higher responder rate is observed in the non-PCG subgroup for either latanoprost or timolol (72% vs 57% and 70% vs 66%, in PP and ITT analysis respectively) compared to PCG subgroup (50% vs 46% and 45% vs 45%, in PP and ITT analysis respectively).

The proportion of responders in the age subgroups followed the same trends observed for mean IOP decreases in these subgroups showing a very low responder rate for the youngest age group 0-<3 yrs for timolol and a reverse tendency in the 3 to <12 yrs old subgroup in which timolol did better.

Discussion and Conclusion on efficacy
Results from this 12 week, non-inferiority study (study A6111137) comparing once daily dose of latanoprost 0.005% versus timolol 0.5% administered twice daily (or 0.25% twice daily for subjects < 3 yrs old) in paediatric patients from 0 to ≤ 18 yrs with glaucoma in at least one eye demonstrate the non-inferiority of latanoprost as a pre-defined margin of -3 mmHg in IOP reduction. Non inferiority should have been still demonstrated if a more stringent non inferiority margin of -1.5 mmHg had been predefined (as it is usually the case in adult studies)

Concerns were raised by the CHMP is terms of the results in patients aged from 0 to <3 yrs since the number of patients included in the studies was very low, a great variability in efficacy, the IOP increase in 2 patients, in addition to the increased systemic absorption observed for this age group (5-7 fold greater than in older children and in adults). These concerns were addressed by the MAH in their responses.
In the paediatric patients aged 0 to < 3 years old, a higher prevalence of PCG is seen. Considering that surgery (e.g. trabeculotomy/goniotomy) is the first line gold standard of care, the CHMP accepted that only a lower number of patients from this age strata could benefit from a medical treatment compared to both older studied age groups. Also the possibility of recruiting in this youngest class was reduced.

In this youngest group, mean (SD) IOP reductions from baseline in the latanoprost and timolol groups were 5.5 (7.11) mmHg and 2.0 (8.77) mmHg, respectively, showing a greater variability in efficacy compared to IOP decreases observed for the 3 to < 12 year age group (6.5 (4.97) mmHg and 7.9 (5.33) mmHg, respectively) and the 12 to 18 year age group (8.6 (7.09) mmHg and 5.9 (4.21) mmHg, respectively). The CHMP agreed that the variability of IOP decrease in the younger age group can be driven by the severity of anatomic abnormality (anterior chamber angle in PCG disease) but also by previous surgical or medical treatments undergone in addition to constraints more likely linked to the young age of patients (lack of cooperation, etc). The analysis of methods used for IOP measurement showed a lack of consistency in 13 subjects of the subgroup < 3 years).
Therefore, this could partly explain the variability observed in IOP decreases in the youngest age group.

Overall, according to literature, which defines success or responder rate for PCG paediatric patients as > 15% IOP decrease from baseline (e.g. Enyedi 2002) or 20% for adults (European Glaucoma Society Guideline), the mean IOP reduction observed at Week 12 in the subgroup of 19 PCG subjects

(including 73% of naïve to glaucoma surgery) and aged 0-<3 (82.4% of subjects in the latanoprost group and 70.6% in the timolol group) continue to demonstrate a clinically relevant IOP decrease from baseline and numeric values are in favour of latanoprost compared to timolol. An additional responder analysis based on a target IOP of 18 mmHg by reference to the Advanced Glaucoma Intervention Study (AGIS) was provided. The results with this more stringent criterion continue to numerically favour latanoprost over timolol.

As regards the IOP increases in 2 PCG subjects (among 5 subjects) < 1 year old at week 12 the MAH provided a complete picture of IOP increases confirming the not unexpected tendency of a higher percentage of patients with an increase in IOP observed in the 0 to <3 year age group for both treatment groups compared to both other age groups reflecting a higher variability of the disease in the younger patients. These results suggest that the greater variability in efficacy of topical eye drops therapies seen in the < 3 year age group is also driven by the character of the disease and pathophysiology.

The MAH provided reassuring evidence of an acceptable safety margin in children less than 3 years of age despite higher systemic exposure. The MTD for the ocular route was estimated to be 11µg/kg. This dose is approximately 275-fold higher than the approved ophthalmic dose. Consequently, the safety margin in adult patients is approximately 275 as well.
Taking into account the higher systemic exposure (5 to 7 fold) evidenced in children < 3 years, the safety margin in this subgroup of patients could be estimated to be 40 to 55 approximately.

Based on the above, latanoprost eye drops in the younger strata of age (mainly PCG subjects) is considered a valuable option to treat also the younger paediatric glaucoma patients.
In this target population, mean IOP decrease from baseline reaches at least 20%, which is considered a relevant percentage of IOP reduction in adults, and that the systemic passage calculation shows an acceptable safety margin estimated to be approximately 40 to 55.
Nevertheless, it is clearly reflected in Section 4.4 and Section 5.1 of the SPC that the data on efficacy and safety in children below 3 years of age is very limited.

Clinical Safety
Clinical safety on paediatric patients is based on the two pivotal studies submitted in this application (an open-label pharmacokinetic study – study A6111139 and a randomised, double-blind, parallel safety and efficacy study – study A6111137). The safety analysis set was performed in all patients who received at least one dose of study medication (ITT population).

Patient exposure
A total of 137 subjects were treated in study A6111137. The number of patients of by age subgroup is shown in Table 8 (below). The median duration of treatment for both treatments groups was 85.0 days.

In study A6111139 a total of 47 patients were exposed for two weeks to latanoprost therapy (8 subjects in the 0 to <3yrs, 10 subjects in the 3 to <12yrs, 7 subjects in the 12 to 18 yrs and 22 in > 18 yrs age group).

Adverse events (AEs)
The most common AEs reported in study A6111137 were nasopharyngitis and headache. The incidence of conjunctival hyperaemia was low. Most AEs were mild or moderate in intensity, severe AEs were reported for 1 patient in the latanoprost group and 4 patients in the timolol group. The below table (table 8) shows all AEs reported in this study.

Table 8 All Adverse Events reported in study A6111137

N	Latanoprost (N=68)	Timolol (N=69)
Pts 0-<3 years old	17	17
Pts 3 - < 12 years old	26	29
Pts 12 – 18 years old	25	23
Number of adverse events	41	64
Pts 0-<3 years old	16	18
Pts 3 - < 12 years old	11	22
Pts 12 – 18 years old	14	24
Patients with AEs	24 (35.3%)	29 (42.0%)
Pts 0-<3 years old	9 (52.9%)	7 (41.2)
Pts 3 - < 12 years old	7 (26.9%)	10 (34.5%)
Pts 12 – 18 years old	8 (32.0%)	12 (52.2%)
Patients with serious AEs	2 (2.9%)	7 (10.1%)
Pts 0-<3 years old	2 (11.8%)	4 (23.5%)
Pts 3 - < 12 years old	0	1 (3.4%)
Pts 12 – 18 years old	0	2 (8.7%)
Patients with severe AEs	1 (1.5%)	4 (5.8%)
Pts 0-<3 years old	1 (5.9%)	2 (11.8%)
Pts 3 - < 12 years old	0	1 (3.4%)
Pts 12 – 18 years old	0	1 (4.3%)
Patients discontinued due to Aes	1 (1.5%)	4 (5.8%)
Pts 0-<3 years old	1 (5.9%)	1 (5.9%)
Pts 3 - < 12 years old	0	1 (3.4%)
Pts 12 – 18 years old	0	2 (8.7%)
Patients with dose reduced or temporary discontinuation due to AEs	0	0
Pts 0-<3 years old	0	0
Pts 3 - < 12 years old	0	0
Pts 12 – 18 years old	0	0

The frequency of the most commonly reported AE is not significantly different for both treatment groups however a trend for higher frequency is seen in the timolol group.

A higher frequency of AEs is noted in patients aged less than 3 yrs treated with latanoprost (53%) than with timolol (41%). This trend is reversed, in patients aged 3 to 12 yrs and 12 to 18 yrs: 27% and 32% of patients respectively, in latanoprost group and 34% and 52% of patients respectively, in timolol group. This difference is explained by the occurrence of many of the AEs in the younger population being associated with infection-related AEs (infection and infestation SOC): 5 (29.4%) in the latanoprost group and 6 (35.4%) in the timolol group. These events are more commonly seen in young paediatric patients while infections in older paediatric patients (more than 3 yrs) were lower.

Treatment-emergent related AEs were reported in 6% of patients treated with latanoprost patients and 14.5% of patients treated with timolol. Most treatment related AEs were mild or moderate in intensity. Conjunctival hyperaemia treatment-related AE was reported in 3 subjects (4.3%) in the timolol group and 0 subjects in the latanoprost group.

In study A6111139 there were no permanent or temporary discontinuations due to AEs, no dose reductions due to AEs, no deaths, no serious AEs nor treatment-emergent AEs reported.

Adverse Events of interest
Ocular tolerability and associated AEs are of interest for medications containing preservatives (e.g. benzalkonium chloride) and requiring chronic administration applicable to paediatric glaucoma patients.

These AEs of special interest include: conjunctival hyperaemia, ocular hyperaemia, photophobia, eye irritation (burning grittiness, itching, stinging and foreign body sensation), punctate keratitis (mostly without symptoms), corneal opacity, allergic conjunctivitis, blepharitis, instillation site pain, and eye pain.

In study A6111137, amongst these specific AEs only one (instillation site pain, study eye) was noted and judged related to the study medication - latanoprost. Only conjunctival hyperaemia and eye pain were amongst the frequently reported AEs of special interest in the paediatric study A6111137.

There were no reports of cystoid macular oedema or asthma reported during this study.

Conjunctival hyperaemia

Is a well known and recognised adverse event of prostaglandins. Most subjects had normal conjunctival hyperaemia scores at baseline and, in most cases scores remained unchanged during the study. Most post-baseline conjunctival hyperaemia scores were mild or moderate (21 of 68 subjects in the latanoprost group and 27 of 69 subjects in the timolol group).

It is noted that worsening of conjunctival hyperaemia (usually only by 1 grade) was reported for 12 subjects (18%) in the latanoprost group and in 10 subjects (14%) in the timolol group. In all age groups, only one case (0 to <3 yrs group) in the latanoprost-treated patients reported a 2-grade worse score. The percentage of worsening hyperaemia scores by age group and treatment is shown in the following table (Table 9).

Age Group	Percentage of worsening hyperemia scores	
	Latanoprost	Timolol
0 to <3	17%	8%
3 to <12	15%	21%
12 to <18	28%	13%

Conjunctival hyperaemia was reported in study eye in 2 patients in the latanoprost group (0 to <3 yrs and 3 to<12yrs age groups) and in 3 patients in the timolol group (2 aged 3 to <12 yrs and 1 in the 12 to <18 yrs). Of the total 5 reported cases of conjunctival hyperaemia, only 3 were considered treatment-related AE and all within timolol group.

Serious adverse events (SAEs) and deaths

No deaths were reported during both studies.

There were no serious AEs reported during study A6111139. In study A6111137, of the 137 subjects exposed: 9 subjects experienced 14 non-fatal SAEs: 2 subjects (2.9%) in the latanoprost group and 7 subjects (10.1%) in the timolol group.

One severe SAE was reported in 1 subject in the latanoprost group (lens dislocation due to trauma), and 6 severe SAEs were reported in 4 subjects in the timolol group, were suspected to be related with study-treatment. These cases occurred in children aged from 9 months to 16 years (3 were 0 < 3 yrs, 1 was between 3 < 12 yrs, and 1 between 12 and < 18 yrs).

Three patients experienced acute glaucoma or decompensation glaucoma, most likely due to a progression of underlying disease, suggesting lack of efficacy. These three patients received timolol twice daily which was permanently discontinued as result of the glaucoma in 2 cases. In the remaining case, timolol was continued unchanged.

Discontinuation due to AEs

Five subjects (1 subject [1.5%] in the latanoprost group and 4 subjects [5.8%] in the timolol group) discontinued the study due to ocular AEs (glaucoma, conjunctival bled and visual acuity decrease). Among these five patients, 3 patients experienced serious AEs (1 in the latanoprost treatment group [pneumonia considered not related to study treatment] and 2 in the timolol treatment group).

Special populations

Patients younger than 1 year

In the latanoprost treatment group, more patients in the 0 to < 3yrs group experienced adverse events (53%), serious AEs (12%), severe AEs (6%) and discontinuation due to AEs (6%) in comparison with other age groups. The following tables present the treatment-emergent AEs for patients ≤ 1yr and for patients ≥ 1 yr of age (Table 10 and Table 11, respectively).

Table 10: Adverse Events (All-Causality) for Age Group 0 - ≤1 Year Old

Preferred Term, MedDRA v. 12.1	Latanoprost N=6 n(%)	Timolol N=7 n(%)
Subjects with serious adverse events	0	1 (14.3%)
Subjects with severe adverse events	0	1 (14.3%)
Subjects with adverse events	4 (66.7%)	2 (28.6%)
Corneal edema-study eye	0	1 (14.3%)
Corneal edema-untreated fellow eye	1 (16.7%)	0
Pyrexia	0	1 (14.3%)
Exanthema subitum	1 (16.7%)	0
Nasopharyngitis	1 (16.7%)	0
Pneumonia	0	1 (14.3%)
Rhinitis	2 (33.3%)	1 (14.3%)
Cough	0	1 (14.3%)
Trabeculetomy-both eyes	0	1 (14.3%)
Number of adverse events	5	6

Table 11. Adverse Events (All-Causality) for Age Group ≥ 1 Year Old Occurring in >2% Subjects

Preferred Term, MedDRA v. 12.1	Latanoprost N=62 n(%)	Timolol N=62 n(%)
Subjects with serious adverse events	2 (3.2%)	6 (9.7%)
Subjects with severe adverse events	1 (1.6%)	3 (4.8%)
Subjects discontinued due to adverse events	1 (1.6%)	4 (6.5%)
Subjects with adverse events	20 (32.3)	27 (43.5)
Conjunctival disorder-both eyes	0	2 (3.2%)
Conjunctival hyperaemia-both eyes	0	3 (4.8%)
Conjunctival hyperaemia-study eye	2 (3.2%)	3 (4.8%)
Visual acuity reduced-study eye	0	2 (3.2%)
Pyrexia	2 (3.2%)	1 (1.6%)
Bronchitis	0	2 (3.2%)
Infuenza	0	4 (6.5%)
Nasopharyngitis	3 (4.8%)	5 (8.1%)
Viral infection	1 (1.6%)	2 (3.2%)
Headache	2 (3.2%)	4 (6.5%)
Number of adverse events	36	58

Overall, the adverse events observed in the ≤1 yr of age group are common infection-related events seen in this paediatric population (exanthema subitum, rhinitis, nasopharyngitis). It is noted that in spite of the 6-7 fold higher systemic exposure seen in patients aged 0 to <3 yrs (study A6111139) no further systemic effects are seen than the other age groups and than in patients on treatment with timolol.

The summary of treatment-emergent AEs in age 0 to <3 yrs group by treatment group distinguishing patients that received timolol 0.25% and timolol 0.5% was provided by the MAH. Due to the small size of this age group of patients no meaningful comparison to the latanoprost reporting rate can be made. Nevertheless, it is noteworthy that the lower dose of timolol (0.25%) caused adverse events in 2 of the 5 treated patients. Overall, this rate (40%) is comparable to the adverse event rate observed in 0 to <3 year age group of timolol (0.5% and 0.25% combined) treated patients (41.2%). The adverse event rate in patients <3 years of age treated with latanoprost is 52.9%.

The potential impact of the presence of benzalkonium chloride 0.02% (BAK) as preservative in eye drops solution of Xalatan was discussed by the MAH at CHMP. Concerns that preservatives can lead to ocular tolerability and adverse events have been recently discussed in an ad-group of experts. Further to this discussion and review of data available, the CHMP in December 2009 concluded that based on the available safety evidence a general recommendation not to use preservatives in eye drops could not be supported. Nevertheless, acknowledging the potential risk, the MAH committed to assess the potential risk of ocular tolerability and ocular surface signs in the proposed long term studies outlined in the RMP.

Post marketing experience
A cumulative search of the MAH's safety database for latanoprost cases reported from 5 June 1996 through 1 December 2009 identified 67 cases as unique medically confirmed, non-clinical study in paediatrics patients. Of these 67 cases, 9 cases were considered serious, 40 non-serious and 18 unknown cases.

The most commonly reported AEs in paediatric patients were: blepharal pigmentation, eye irritation, growth of eyelashes, iris hyper pigmentation, ocular hyperaemia, asthma, and dyspnea. Two cases amongst the 4 cases of dyspnea took timolol as concomitant medication. The patients who develop asthma had prior medical history.

Amongst the 9 serious cases, one case of conjunctivitis, one of IOP increase, one of choiroidal detachment, one of drug administration error and one case of episcleritis had been observed and resolved.

In a neonate exposed during pregnancy, oesophageal atresia and development delay were observed. Additionally, one case of retinal detachment and one case of lung disorder were reported. These three cases had an unknown outcome. The remaining case was of hyperaemia which resolved with sequelae.

According to the limited data available in children, the safety profile of latanoprost in this population does not seem very different compared to the safety profile in adults.

Additional safety information
Supporting safety information in adults was provided by the MAH. Data from 3 controlled clinical studies in adults were compared with the randomised paediatric study (A6111137). The number of paediatric patients was very limited compared to adult population.

In these 3 adult clinical studies, a higher frequency of AEs in latanoprost group compared to timolol group is noted, opposite to paediatric studies. Table 12 below summarises these observations.

Table 12. Summary of Most Common All-Causality Treatment-Emergent Adverse Events (in >2% Subjects) in Adults and Children

Preferred term	Latanoprost		Timolol	
	Adults N = 184 n (%)	Children N = 68 n (%)	Adults N = 179 n (%)	Children N = 69 n (%)
Irritation eye[a]	35 (19.0)	0	17 (9.5)	0
Eye hyperaemia/ocular hyperaemia	16 (8.7)	1 (1.5)	6 (3.4)	0
Conjunctival hyperaemia	0	3 (4.4)	0	6 (8.7)
Conjunctival disorder	8 (4.3)	0	7 (3.9)	2 (2.9)
Conjunctivitis[b]	6 (3.3)	2 (2.9)	8 (4.5)	3 (4.3)[c]
Eye pain	4 (2.2)	1 (1.5)	4 (2.2)	0
Vision abnormal	23 (12.5)	0	18 (10.1)	0
Corneal disorder	7 (3.8)	0	13 (7.3)	2 (2.9)[d]
Blepharitis	11 (6.0)	0	7 (3.9)	0
Cataract	10 (5.4)	0	8 (4.5)	0
Errors of refraction	7 (3.8)	0	9 (5.0)	0
Increased iris pigmentation	8 (4.3)	0	3 (1.7)	0
Increased intraocular pressure	6 (3.3)	1 (1.5)	2 (1.1)	1 (1.4)
Visual field defect	5 (2.7)	0	6 (3.4)	0
Visual acuity reduced	0	0	0	2 (2.9)
Upper respiratory tract infection	9 (4.9)	0	15 (8.4)	1 (1.4)
Arthritis	4 (2.2)	0	4 (2.2)	0
Dizziness	4 (2.2)	0	0	1 (1.4)
Depression	5 (2.7)	0	1 (0.6)	0
Hypercholesterolaemia	4 (2.2)	0	0	0
Hypertension	3 (1.6)	0	6 (3.4)	0
Sinusitis	5 (2.7)	0	3 (1.7)	0
Influenza-like symptoms	0	0	4 (2.2)	0
Headache	4 (2.2)	2 (2.9)	4 (2.2)	4 (5.8)
Nasopharyngitis	0	4 (5.9)	0	5 (7.2)
Pyrexia	0	2 (2.9)	0	2 (2.9)
Influenza	0	0	0	4 (5.8)
Rhinitis	2 (1.1)	2 (2.9)	0	1 (1.4)
Viral infection	0	1 (1.5)	0	2 (2.9)
Bronchitis	2 (1.1)	0	1 (0.6)	2 (2.9)

Abbreviations: n = number of subjects included in assessment, N = number of subjects in population, CSR = Clinical Study Report
[a] Irritation eye includes events related to burning, stinging and itching.
[b] Conjunctivits includes allergic, bacterial and viral conjunctivitis
[c] Includes 1 subject with hyperaemia in study eye and fellow eye reported separately, 1 subject with hyperaemia in both eyes, and 1 subject with hyperaemia in study eye.
[d] Includes 1 subject with corneal opacity in study eye and corneal perforation in fellow eye, as well as 1 subject with corneal pigmentation in study eye.

The most commonly adverse events in paediatric patients treated when compared with adults were noted: conjunctival hyperaemia, nasopharyngitis and pyrexia. These AEs were few and equally distributed across all paediatric age groups on treatment with latanoprost.

It should be noted that the occurrence of malignant melanoma reported in adults is under closely review by the CHMP Pharmacovigilance Working Party following a cluster of cases described in the literature (Estève et al. Mélanomes associés au latanoprost: trois cas. Ann Dermatol Venereol. 2009; 136 (1):60-1). In April 2010, the working party concluded that current scientific evidence is insufficient to support a causal association between latanoprost and malignant melanoma but kept under close monitoring.

No ocular melanoma was reported in this (short term) paediatric study (A6111137), which included a limited number of patients, but this potential risk is reflected in the Risk Management.
Other relevant AEs in adult population (herpetic keratitis, iris cyst, iris pigmentation, malignant melanoma, cystoids macular oedema and ocular tolerability) should be kept under very close monitoring in paediatric patients, although no cases were reported in the paediatric study.

Discussion and Conclusion on safety
Safety data in paediatric patients i.e. data from the pharmacokinetic (A6111137) and clinical (A6111139) studies, and from post-marketing data seems to suggest that the safety profile of latanoprost, (0.005%, eye drops solution, once daily) in paediatric patients reflects the safety profile known for adult patients. However, it should be noted that the number of subjects included in the paediatric studies is low and that these are short term studies.

Nevertheless, in paediatric patients it is noted a slightly higher reporting rate of conjunctival hyperaemia, nasopharygitis and pyrexia in comparison with adults and this should be noted in the SmPC.

A higher frequency of AEs noted in patients aged less than 3 yrs treated with latanoprost (53%) than with timolol (41%). This trend is reversed, in patients aged 3 to 12 yrs and 12 to 18 yrs: 27% and 32% of patients respectively, in latanoprost group and 34% and 52% of patients respectively, in timolol group.

In the latanoprost treatment group, more patients in the 0 to < 3yrs group experienced adverse events (53%), serious AEs (12%), severe AEs (6%) and discontinuation due to AEs (6%) in comparison with other age groups.

This difference is explained by the occurrence of many of the AEs in the younger population being associated with infection-related AEs (infection and infestation SOC): 5 (29.4%) in the latanoprost group and 6 (35.4%) in the timolol group. These events are more commonly seen in young paediatric patients while infections in older paediatric patients (more than 3 yrs) were lower.

Uncertainties in terms of the long-term safety profile in paediatric patients would be addressed in the long-term safety follow-up studies that the MAH will perform. These studies are expected to provide information on the effect of latanoprost on eyelash growth, iris pigmentation and stimulation on melanogenese in paediatrics population that could not have been observed in the clinical study A6111137 with limited duration.

2.4. Pharmacovigilance

Detailed Description of the Pharmacovigilance System (DDPS)
The CHMP having considered the Pharmacovigilance system as described in this application and the responses provided in writing by the MAH, agreed that the system in place fulfils the legislative requirements.

However, the MAH within the next updated version of the DDPS will make clear that adverse drugs reactions are reported to the National Competent Authorities within the legal timelines and will include information with regard to the absolute frequency or maximum time interval between audits for the Pharmacovigilance system for Drug Safety and Surveillance (DSS).

Risk Management Plan (RMP)

A RMP in accordance with the "Guideline on Risk management systems for medicinal products for human use" (EMEA/CHMP/96268/2005) was submitted. This is the first RMP developed for Xalatan and associated names.

Table Summary of the risk management plan

Safety concerns	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Identified Risks		
Conjunctival Hyperaemia	Routine Pharmacovigilance	Routine pharmacovigilance including labeling, event assessment and reviews. The event is monitored as part of routine pharmacovigilance including event assessment and aggregate reporting. Labeling: Section 4.8 lists mild to moderate conjunctival hyperaemia as a very common event.
Eyelash and Vellus Hair Changes	Routine Pharmacovigilance	Routine pharmacovigilance including labeling, event assessment and reviews. The event is monitored as part of routine pharmacovigilance including event assessment and aggregate reporting. Labeling: Special warning and precaution in section 4.4 of the SPC provides information on the gradual change in eyelash or vellus hair with the use of latanoprost. Section 4.8 lists eyelash and vellus hair changes as very common events.
Periorbital Skin Discoloration	Routine Pharmacovigilance	Routine pharmacovigilance including labeling, event assessment and reviews. The event is monitored as part of routine pharmacovigilance including event assessment and aggregate reporting. Labeling: Special warning and precaution in section 4.4 of the SPC provides information on periorbital skin discolouration. Section 4.8 lists darkening of the palperbral skin of the eyelids as a rare event.
Iris Hyperpigmentation	Routine Pharmacovigilance	Routine pharmacovigilance including labeling, event assessment and reviews. The event is monitored as part of routine pharmacovigilance including event assessment and aggregate reporting. Labeling: Special warning and precaution in section 4.4 of the SPC provides information on iris hyperpigmentation. Section 4.8 lists iris pigmentation as a very common event

Potential Risks		
Cystoid Macular Oedema	Routine Pharmacovigilance	Routine pharmacovigilance including labeling, event assessment and reviews. The event is monitored as part of routine pharmacovigilance including event assessment and aggregate reporting. Labeling: Special warning and precaution in section 4.4 of the SPC states reports of macular oedema have occurred mainly in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema (such as diabetic retinopathy and retinal vein occlusion). Xalatan should be used with caution in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema. In section 4.8, macular oedema is listed as a rare event under eye disorders.
Aggravation of Asthma	Routine Pharmacovigilance	Routine pharmacovigilance including labeling, event assessment, and reviews. The event is monitored as part of routine pharmacovigilance including event assessment and aggregate reporting. Labeling: Special warning and precautions in section 4.4 of the SPC states that there is limited experience from patients with asthma, but some cases of exacerbation of asthma and/or dyspnoea were reported in post marketing experience. Therefore, asthmatic patients should be treated with caution until there is sufficient experience with this event. In section 4.8, asthma, and asthma exacerbation are listed as rare events under respiratory, thoracic and mediastinal disorders. Information is provided in section 5.1 states that latanoprost in clinical doses has not been found to have any significant pharmacological effects on the cardiovascular or respiratory system
Ocular and cutaneous melanoma	Routine Pharmacovigilance	Routine pharmacovigilance including labeling, event assessment, and reviews. The events are monitored as part of routine pharmacovigilance including event assessment and aggregate reporting.
Missing Data		
Ocular tolerability in paediatric population	Routine Pharmacovigilance	Special warnings and precautions in section 4.4 of the SPC states that long-term safety in children has not yet been established.
Long Term Safety in paediatric population	Routine Pharmacovigilance	Special warnings and precautions in section 4.4 of the SPC states that long-term safety in children has not yet been

		established.
Limited experience with patients with asthma	Routine Pharmacovigilance	Labeling: Special warning and precautions in section 4.4 of the SPC states that there is limited experience from patients with asthma, but some cases of exacerbation of asthma and/or dyspnoea were reported in post marketing experience. Therefore, asthmatic patients should be treated with caution until there is sufficient experience with this event. In section 4.8, asthma, and asthma exacerbation are listed as rare events under respiratory, thoracic and mediastinal disorders. Information is provided in section 5.1 states that latanoprost in clinical doses has not been found to have any significant pharmacological effects on the cardiovascular or respiratory system

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information. However, it was agreed that the risk of drug interactions in paediatric patients should be carefully followed within the RMP as important missing information.

In addition to the routine Pharmacovigilance activities, a post-authorisation study programme in order to evaluate long-term safety profile of Xalatan in paediatric populations was agreed by the CHMP *as per* stated in the PIP. The programme comprehends a combination of a 3-year study (A6111143) and a 7-year enhanced surveillance programme (A6111144).

Study A6111143 will evaluate the long-term impact of treatment with Xalatan on ocular development, ocular neurodegenerative disease, hyperpigmentation changes in the eye, corneal endothelial function/corneal thickness, and ocular tolerability by comparing paediatric subjects treated with latanoprost with those not treated with latanoprost or other prostaglandin analogues.

It was agreed that cystoid macular oedema will be assessed using the study AE report page in the case report form (CRF). The final version of the CRF will be annexed to the study protocol. In addition, the MAH will present a discussion whether the OCT technique can be recommended in the protocol's Appendix 1 "recommended assessment methods". A comparison between macular oedema reported in aphakin and non-aphakin patients will be performed in the PASS studies. An estimation of the mean exposure to latanoprost expected in the PASS studies will be submitted.

Study A6111144, is an active surveillance programme to collect AEs of special interest such as hyperpigmentation changes in the eye among paediatric patients treated with Xalatan over a subsequent 7-year period. The full study protocol will be provided and in this regard the MAH will provide the timelines for the submission of the protocol.

The next updated version of the RMP will include all relevant documents and amendments to reflect the above agreed. In this regard, the table summary of the EU RMP will be revised to reflect the PASS studies as additional Pharmacovigilance activity and the drug interactions as missing information.

Periodic Safety Updated Reports (PSURs)

A PSUR should be submitted every 6-months during the first 2 years of the EC granting of this extension of indication for paediatric patients, then yearly.
In addition, the PSURs should include a separate review on drug interaction in the paediatric population and on the current and lost to follow up numbers in PASS.

3. Benefit risk assessment

Benefits

Xalatan, latanoprost 0.005% ophthalmic solution used in a paediatric population from 0 to <18yrs has been shown non-inferiority to timolol 0.5% (and where used 0.25%) in the reduction of IOP associated paediatric pathologies.

Primary analysis

All analyses on the primary endpoint are consistent demonstrating that the primary objective of non inferiority is reached.

All the results observed from either the primary efficacy analysis using the pre-specified ANCOVA model (with LOCF), or additional confirmatory analysis using the reduced ANCOVA model or the ANOVA model but also sensitivity analyses show a similar trend in results. The results of the ITT analyses were also consistent with the PP analyses confirming that non-inferiority to timolol can be accepted for latanoprost for the overall PP population.

All the lower bounds of the 95% CI of the difference between the LS means were well above the pre-defined non inferiority margin of -3 mmHg agreed by PDCO but also above -1.5 mmHg. Therefore, a non inferiority should have been still demonstrated if a more stringent non inferiority margin of 1.5 mmHg had been predefined as it is usually done in adult studies.

Secondary analyses provide results in accordance with primary analysis

Mean IOP reductions range from 6.7 to 7.8 mm Hg in the latanoprost arm versus 5.3 to 6.9 mm Hg in the timolol arm which fairly reflects the expectations (6-7 mm Hg in mean IOP reduction from baseline) based on historical results. As a reminder, historical reference were from the 3 pivotal studies carried out in adults for latanoprost and from the dorzolamide study conducted in paediatric glaucoma population; all studies included comparisons with timolol. Therefore, the sought external consistency with the historical results is confirmed. This consistency is of importance as the paediatric study did not include a placebo arm due to ethic reasons that were accepted by the PDCO. Similarly, the internal consistency with the comparator (timolol) is demonstrated showing comparable IOP reductions in both latanoprost and timolol treatment groups. Mean IOP reductions in the latanoprost group were numerically slightly greater than in the timolol group at each study visit (Weeks 1, 4, and 12) suggesting a tendency in favour of latanoprost which can be considered well in line with the tendency reported in adults. Nevertheless, these results only demonstrate a non inferiority to timolol and do not show a statistical superiority of latanoprost over timolol.

Again, all the analyses regarding IOP reductions were consistent in both PP and ITT populations.

Also according to these results, IOP appears to quickly decrease within the first week of treatment and to remain approximately stable up to the 12-week duration of the study. This observation reinforces the relevance of comparing figures of IOP reduction at Week 12 in paediatric study with figures at 3-Month from historical adult Studies (9200PG004, 9200PG005 and 9200PG006) as provided by the MAH since the major part of the IOP decrease is reached as early as after one week of treatment.

All responder rates (proportion of subjects with a 15% or more IOP reduction at both Weeks 4 and 12) were > 50%. Numeric trends in responder rate difference (without statistical significant) were in favour of latanoprost 0.05 % group in both PP population (60% vs. 52%, for latanoprost and timolol, respectively) and ITT population (59% vs. 57%, for latanoprost and timolol, respectively).

This confirms that mean IOP decreases observed in both treatment groups are of acceptable clinical relevance.

In the infant group it has been shown to be potentially better than timolol. Latanoprost provided evidence for better reduction in IOP than timolol in those patients without PCG. As expected, a higher responder rate was also observed in the non-PCG subgroup compared to PCG subgroup.

Risks

Xalatan, latanoprost 0.005% ophthalmic solution used in a paediatric population from 0 to <18yrs has been shown to have different pharmacokinetic characteristics in the 0 to <3yrs olds and 3 to <12 yrs olds when considering Cmax and AUC. In the 0 to <3yrs old group Cmax was 6-fold higher and AUC 7-fold higher than the adult population. In the 3 to <12yrs old these parameters were 2-fold higher. The elimination time is the same in all populations studied. The increase exposure in the 0 to <3yrs old population is still well below the maximal tolerability threshold seen in adults. No serious adverse

events which could be linked to this higher systemic concentration seen in infants and young children were noted.

In paediatric patients it is noted a slightly higher reporting rate of nasopharygitis and pyrexia in comparison with adults and this is noted in the SmPC.

Due to the limited duration of both pharmacokinetic and clinical studies, the long term safety profile of latanoprost in the paediatric population remains to be further studied as an effect of latanoprost on eyelash growth, iris pigmentation and stimulation on melanogenese in paediatrics population cannot be eliminated with long term treatment.

Although there is very limited data available in children, the safety profile of latanoprost in this population does not seem very different compared to the safety profile in adults. The specific body systems associated with events in the paediatric trials include the 'nervous system disorders', the 'infections and infestations', and 'eye disorders' reflecting inter current illnesses that are common among paediatric patients or other AES already described in the product information. No new signals have been raised. However, caution is advised due to the low number of patients enrolled in this paediatric study with limited duration. However, due to the low number of paediatric patients, even though it seems that the safety profile in the paediatric population is comparable to the known AEs for the adult population, and it is consistent with the current SmPC, no firm and definitive conclusion can be drawn, especially when the long term use.

Benefit-Risk Balance

The benefit risk balance is in favour of the use of latanoprost 0.005% ophthalmic solution in a paediatric population from 0 to <18yrs.

However, in children from 0 to < 3 years old) that mainly suffers from PCG, surgery (e.g. trabeculotomy/goniotomy) remains the first line treatment.

3.1. Changes to the Product Information

Further to evaluation of all data available, the CHMP agreed with the below indication for Xalatan and associated names:

> *Reduction of elevated intraocular pressure in paediatric patients with elevated intraocular pressure and paediatric glaucoma.*

which is reflected in section 4.1 of the SmPC. Further sections of the SmPC (section 4.2, 5.1) are consequently amended.

Special warnings and precautions for use section (section 4.4) of the SmPC is amended to reflect the limitation of the data available and that long-term data will be collected post-authorisation. The interactions section (section 4.5) is amended to state that interaction studies have so far only been carried out in adults. Section 4.8 (undesirable effects) is updated to reflect the safety profile seen in paediatric patients is similar to the one for adults. Pharmacokinetic results from study A6111139 were reflected in section 5.2.

The package leaflet changes reflect the amendments agreed for the SmPC. Detailed changes can be found in Annex 9.

3.2. Significance of paediatric studies

As none of the studies included in the PIP for Xalatan and associated names was initiated before and completed after 26 January 2007, significance was not assessed.

3.3. Overall conclusion and recommendation

Based on overall submitted data on safety and efficacy provided by the MAH, the CHMP considered by consensus that the risk-benefit balance of Xalatan and associated names for reduction of elevated intraocular pressure in paediatric patients with elevated intraocular pressure and paediatric glaucoma was favourable and therefore recommended amendments to the marketing authorisations of the medicinal product referred to in Annex I of the Opinion.

The relevant sections of the Summary of Product Characteristics and package leaflet are set out in Annex II to the opinion.

The conditions affecting the Marketing Authorisations considered essential for the safe and effective use of the medicinal product, including pharmacovigilance are set out in Annex III.

Furthermore, the agreed Paediatric Investigation Plan is fully completed. The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.