ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCT, ROUTES OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State EU/EEA	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration	Content
Austria	Pfizer Corporation Austria Ges.m.b.H. Floridsdorfer Hauptstrasse 1 A - 1210 Wien, Austria	Xalatan	0.005% w/v	Eye drops, solution	Ocular use	2.5 ml
Belgium	Pfizer SA Boulevard de la Plaine 17 B-1050 Brussels, Belgium	Xalatan	0,005%	Eye drops, solution	Ocular use	2.5 ml
Bulgaria	Pfizer Enterprises SARL, Rond-point du Kirchberg, 51, Avenue J.F. Kennedy, L-1855 Luxembourg, G. D. of Luxembourg	Xalatan	50 micrograms/ ml	Eye drops, solution	Topical use	2.5 ml
Czech Republic	Pfizer. s r.o., Stroupežnického 17, 150 00 Prague 5, Czech Republic	Xalatan	0.005% w/v	Eye drops, solution	Topical use	2.5 ml
Denmark	Pfizer ApS, Lautrupvang 8, 2750 Ballerup, Denmark	Xalatan	50 microg/ ml	Eye drops, solution	Topical use	2.5 ml
Estonia	Pfizer Enterprises SARL 51, Avenue J.F. Kennedy Rond-Point du Kirchberg L-1855 Luxembourg	Xalatan	50 micrograms / ml	Eye drops, solution	Ocular use	2.5 ml
Finland	Pfizer Oy, Tietokuja 4, 00330 Helsinki, Finland	Xalatan	50 microg/ml	Eye drops, solution	Topical use	2.5 ml
France	Pfizer Holding France	Xalatan	0.005% w/v	Eye drops, solution	Topical use	2.5 ml

Member State EU/EEA	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration	Content
	23-25 Avenue du Docteur Lannelongue 75014 Paris France					
Germany	Pharmacia GmbH Linkstraße 10 10785 Berlin, Germany	Xalatan	0.005% w/v	Eye drops, solution	Ocular use	2.5 ml
Germany	Pharmacia GmbH, Linkstraße 10 10785 Berlin, Germany	Latanoprost Pharmacia & Upjohn	0.005% w/v	Eye drops, solution	Ocular use	2.5 ml
Greece	Pfizer Hellas A. E. 243, Messoghion Ave., 154 51 Neo Psychiko, Athens, Greece	Xalatan	50mcg/ ml	Eye drops, solution	Topical use	2.5 ml
Hungary	Pfizer KFT, 1123 Budapest, Alkotás u. 53. MOM Park "F" Ép., Hungary	Xalatan	0.05 mg/ml	Eye drops, solution	Topical use	2.5 ml
Iceland	Pfizer ApS, Lautrupvang 8, 2750 Ballerup, Denmark	Xalatan	50 microg/ ml	Eye drops, solution	Topical use	2.5 ml
Ireland	Pharmacia Ireland Limited 9 Riverwalk National Digital Park Citywest Business Campus Dublin 24 Ireland	Xalatan	0.005% w/v	Eye drops, solution	Topical use	2.5 ml
Italy	Pfizer Italia S.r.l. Via Isonzo, 71 04100 Latina - Italy	Xalatan	0,005	Eye drops, solution	Topical use	2.5 ml

Member State EU/EEA	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration	Content
Latvia	Pfizer Europe MA EEIG, Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom	Xalatan	0.005% w/v	Eye drops, solution	Topical use	2.5 ml
Lithuania	Pfizer Europe MA EEIG Ramsgate Road Sandwich, Kent CT13 9NJ United Kingdom	Xalatan	0.005% w/v	Eye drops, solution	Ocular use	2.5 ml
Luxembourg	Pfizer SA Boulevard de la Plaine 17 B-1050 Brussels, Belgium	Xalatan	0,005%	Eye drops, solution	Ocular use	2.5 ml
Malta	Pfizer Hellas S.A. 243, Messoghion Ave., 154 51 Neo Psychiko, Athens, Greece	Xalatan	0.005% w/v	Eye drops, solution	Topical use	2.5 ml
Netherlands	Pfizer bv Rivium Westlaan 142 2909 LD Capelle a/d IJssel The Netherlands	Xalatan	50 microgram/ml	Eye drops, solution	Topical use	2.5 ml
Norway	Pfizer AS Pb. 3 1324 Lysaker Norway	Xalatan	0.005% w/v	Eye drops, solution	Topical use	2.5 ml
Poland	Pfizer Europe MA EEIG, Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom	Xalatan	0.005% w/v	Eye drops, solution	Ocular use	2.5 ml

Member State EU/EEA	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical Form	Route of administration	Content
Portugal	Laboratorios Pfizer, Lda., Lagoas Park, Edifício 10, 2740-271 Porto Salvo, Portugal	Xalatan	0.005% w/v	Eye drops, solution	Topical use	2.5 ml
Romania	Pfizer Europe MA EEIG, Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom	Xalatan	0.005% w/v	Eye drops, solution	Ocular use	2.5 ml
Slovak Republic	Pfizer Europe MA EEIG, Ramsgate Road, Sandwich, Kent, CT13 9NJ, United Kingdom	Xalatan	0.005% w/v	Eye drops, solution	Topical use	2.5 ml
Slovenia	Pfizer Luxembourg SARL, 51, Avenue J. F. Kennedy, L-1855 Luxembourg, Luxembourg	Xalatan 50 mikrogramov/ml kapljice za oko, raztopina	0.005% w/v	Eye drops, solution	Topical use	2.5 ml
Spain	Pfizer, S.A. Avda. de Europa 20B Parque Empresarial la Moraleja 28108 Alcobendas, (Madrid) Spain	Xalatan	0.005% w/v	Eye drops, solution	Ocular use	2.5 ml
Sweden	Pfizer AB Vetenskapsvagen 10, SE 191 90 Sollentuna Sweden	Xalatan	0.005% w/v	Eye drops, solution	Topical use	2.5 ml
United Kingdom	Pfizer Limited Ramsgate Road Sandwich, Kent CT13 9NJ United Kingdom	Xalatan	0.005% w/v	Eye drops, solution	Topical use	2.5 ml

ANNEX II

AMENDMENTS TO THE SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET

THESE AMENDMENTS TO THE SPC AND PACKAGE LEAFLET ARE VALID AT THE TIME OF THE COMMISSION DECISION.

AFTER THE COMMISSION DECISION THE MEMBER STATE COMPETENT AUTHORITIES WILL UPDATE THE PRODUCT INFORMATION AS REQUIRED.

AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE SUMMARY OF PRODUCT CHARACTERISTICS FOR XALATAN AND ASSOCIATED NAMES (*as per* Annex I)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[…]

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

4.2 Posology and method of administration

[…]

Paediatric population:

{Invented name} eye drops may be used in paediatric patients at the same posology as in adults. No data are available for preterm infants (less than 36 weeks gestational age). Data in the age group < 1 year (4 patients) are very limited (see Section 5.1).

4.4 Special warnings and precautions for use

[…]

Paediatric population

Efficacy and safety data in the age group < 1 year (4 patients) are very limited (see Section 5.1). No data are available for preterm infants (less than 36 weeks gestational age).

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

Long-term safety in children has not yet been established.

4.5 Interaction with other medicinal products and other forms of interaction

[…]

Paediatric population

Interaction studies have only been performed in adults.

4.8 Undesirable effects

[…]

Paediatric Population

In two short term clinical trials (≤ 12 weeks) involving 93 (25 and 68) paediatric patients the safety profile was similar to that in adults and no new adverse events were identified. The short term safety profiles in the different paediatric subsets were also similar (see Section 5.1). Adverse events seen more frequently in the paediatric population as compared to adults are: nasopharyngitis and pyrexia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

[…]

Paediatric population

The efficacy of latanoprost in paediatric patients ≤18 years of age was demonstrated in a 12-week, double-masked clinical study of latanoprost compared with timolol in 107 patients diagnosed with ocular hypertension and paediatric glaucoma. Neonates were required to be at least 36 weeks gestational age. Patients received either latanoprost 0.005% once daily or timolol 0.5% (or optionally 0.25% for subjects younger than 3 years old) twice daily. The primary efficacy endpoint was the mean reduction in intraocular pressure (IOP) from baseline at Week 12 of the study. Mean IOP reductions in the latanoprost and timolol groups were similar. In all age groups studied (0 to <3 years, 3 to <12 years and 12 to 18 years of age) the mean IOP reduction at Week 12 in the latanoprost group was similar to that in the timolol group. Nevertheless, efficacy data in the age group 0 - < 3 year old were based on only 13 patients for latanoprost and no relevant efficacy was shown from the 4 patients representing the age group 0 -< 1 year old in the clinical paediatric study. No data are available for preterm infants (less than 36 weeks gestational age).

IOP reductions among subjects in the primary congenital/infantile glaucoma (PCG) subgroup were similar between the latanoprost group and the timolol group. The non-PCG (e.g. juvenile open angle glaucoma, aphakic glaucoma) subgroup showed similar results as the PCG subgroup.

The effect on IOP was seen after the first week of treatment and was maintained throughout the 12 week period of study, as in adults.

Table: IOP reduction (mmHg) at week 12 by active treatment group and baseline diagnosis

	Latanoprost N=53		**Timolol N=54**	
Baseline Mean (SE)	27.3 (0.75)		27.8 (0.84)	
Week 12 Change from Baseline Mean[†](SE)	-7.18 (0.81)		-5.72 (0.81)	
p-value *vs.* timolol	0.2056			
	PCG N=28	**Non-PCG N=25**	**PCG N=26**	**Non-PCG N=28**
Baseline Mean (SE)	26.5 (0.72)	28.2 (1.37)	26.3 (0.95)	29.1 (1.33)
Week 12 Change from Baseline Mean[†](SE)	-5.90 (0.98)	-8.66 (1.25)	-5.34 (1.02)	-6.02 (1.18)
p-value vs. timolol	0.6957	0.1317		

SE: standard error.

[†]Adjusted estimate based on an analysis of covariance (ANCOVA) model.

5.2 Pharmacokinetic properties

[…]

Paediatric population

An open-label pharmacokinetic study of plasma latanoprost acid concentrations was undertaken in 22 adults and 25 paediatric patients (from birth to < 18 years of age) with ocular hypertension and glaucoma. All age groups were treated with latanoprost 0.005%, one drop daily in each eye for a minimum of 2 weeks. Latanoprost acid systemic exposure was approximately 2-fold higher in 3 to <12 year olds and 6-fold higher in children <3 years old compared with adults, but a wide safety margin for systemic adverse effects was maintained (see section 4.9). Median time to reach peak plasma concentration was 5 minutes post-dose across all age groups. The median plasma elimination half-life was short (<20 minutes), similar for paediatric and adult patients, and resulted in no accumulation of latanoprost acid in the systemic circulation under steady-state conditions.

AMENDMENTS TO BE INCLUDED IN THE RELEVANT SECTIONS OF THE PACKAGE LEAFLET FOR XALATAN AND ASSOCIATED NAMES (*as per* Annex I)

The following text highlighted in bold should be reflected in the relevant sections of the package leaflet, as relevant.

If you have any further questions, ask your doctor **or the doctor treating your child** or your pharmacist.

This medicine has been prescribed for you **or for your child**. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor **or the doctor treating your child** or your pharmacist.

1. WHAT IS {INVENTED NAME} AND WHAT IS IT USED FOR?

[…]
{Invented name} is also used to treat increased eye pressure and glaucoma in all ages of children and babies.

2. BEFORE YOU USE {INVENTED NAME}

{Invented name} can be used in adult men and women (including the elderly) **and in children from birth to 18 years of age. {Invented name} has not been investigated in prematurely born infants (less than 36 weeks gestation).**

Take special care with {INVENTED NAME}

Talk to your doctor, **or the doctor treating your child** or your pharmacist before you take {Invented name} **or before you give this to you child** if you think any of the following apply to you **or your child**:

If you **or your child** are about to have or have had eye surgery (including cataract surgery)

If you **or your child** suffer from eye problems (such eye pain, irritation or inflammation, blurred vision)

If you **or your child** suffers from dry eyes

If you **or your child** have severe asthma or the asthma is not well controlled

If you **or your child** wear contact lenses. You can still use{Invented name}, but follow the instruction for contact lens wearers in Section 3

Taking other medicines

{Invented name} may interact with other medicines. Please tell your doctor, **the doctor treating your child** or pharmacist if you **or your child** are taking or have taken any other medicines including those medicines (or eye drops) obtained without a prescription.

Important information about some of the ingredients of {Invented name}

[…]
If you **or your child** wear contact lenses, they should be removed before using {Invented name}. After using {Invented name} you should wait 15 minutes before putting the contact lenses back in. See the instructions for contact lens wearers in Section 3.

3. HOW TO USE {INVENTED NAME}

Always use {Invented name} exactly as your doctor, **or the doctor treating your child** has told you. You should check with your doctor, **or the doctor treating your child** or pharmacist if you are not sure.

The usual dosage for adults (including the elderly) **and children** is one drop once a day in the affected eye(s). The best time to do this is in the evening. Do not use Xalatan more than once a day, because the effectiveness of the treatment can be reduced if you administer it more often.

Use Xalatan as instructed by your doctor, **or the doctor treating your child** until they tell you to stop.

Contact lens wearers

If you **or your child** wear contact lenses, they should be removed before using Xalatan. After using Xalatan you should wait 15 minutes before putting the contact lenses back into the eyes.

If you use more {Invented name} than you should

If you put too many drops into the eye, it may lead to some minor irritation in the eye and the eyes may water and turn red. This should pass, but if you are worried contact your doctor **or the doctor treating your child** for advice.

Contact your doctor as soon as possible if you **or your child** swallows {Invented name} accidentally.

If you stop using {Invented name}

You should speak to your doctor **or the doctor treating your child** if you want to stop taking Xalatan.

4. POSSIBLE SIDE EFFECTS

[…]
Side effects seen more often in children compared to adults are runny itchy nose and fever.

ANNEX III

CONDITIONS OF THE MARKETING AUTHORISATION(S)

National Competent Authorities (NCAs), coordinated by the Reference Member State where applicable, shall ensure that the following conditions are fulfilled by the Marketing Authorisation Holders (MAHs):

- Within the next updated version of the Detailed Description of the Pharmacovigilance System (DDPS) the MAH will:

  - make clear/provide reassurance that Adverse Drug Reactions are transmitted to NCAs within the legal timelines;
  - include information with regard to the absolute frequency or maximum time interval between audits for the Pharmacovigilance system for Drug Safety and Surveillance.

  The next updated version of the DDPS should be submitted together with the 6-monthly Periodic Safety Updated Report (PSUR) due after the European Commission decision.

- The next updated version of the Risk Management Plan (RMP) will have to include all relevant annexed documents and amendments to reflect the following:

  - Risk of drug interactions in paediatric patients as important missing information;
  - Cystoid macular oedema assessment using the study Adverse Event (AE) report page in the case report form (CRF). The final version of the CRF will be annexed to the study A6111143 protocol;
  - The MAH discussion whether the OCT (optical coherence tomography) technique can be recommended in the protocol's Appendix 1 "recommended assessment methods";
  - The PASS (Post-Authorisation Safety) studies will include a comparison between macular oedema reported in aphakin and non-aphakin patients;
  - An estimation of the mean exposure to latanoprost expected in the PASS studies will be submitted;
  - The timelines for the submission of the full study A6111144 protocol;
  - Revised table summary of the EU RMP to reflect the PASS studies as additional Pharmacovigilance activities and the drug interactions as missing information.

  The next updated version should be submitted together with the 6-monthly PSUR due after the European Commission decision.

- Submission of a 6-monthly Period Safety Updated Report (PSUR) during the first 2 years following the European Commission decision and then after yearly;

- The PSURs will include a separate review on drug interaction in the paediatric population and on the current and lost to follow up numbers in PASSs;