Safeguarding public health

Public Assessment Report

Decentralised Procedure

Latanoprost 0.005%w/v Eye Drops, Solution

Latanoprost

UK/H/2237/001/DC

UK licence no: PL 20254/0038

Orifarm Generics A/S

Medicines and Healthcare products Regulatory Agency

Latanoprost 0.005% w/v Eye Drops, Solution

PL 20254/0038

LAY SUMMARY

On 20th October 2010, Denmark, Germany, Finland, Norway and Sweden and the UK agreed to grant a marketing authorisation to Orifarm Generics A/S for the medicinal product Latanoprost 0.005% w/v Eye drops, Solution. The marketing authorisation was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, a licence was granted in the UK on 16th December December 2010.

Latanoprost belongs to a group of medicines called prostaglandins. It works by increasing the natural outflow of fluid from inside the eye in to the bloodstream.

Latanoprost eye drops are used to treat conditions known as open angle glaucoma and ocular hypertension. Both of these conditions are linked with an increase in the pressure within your eye, eventually affecting your eye sight.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Latanoprost 0.005% w/v Eye drops, Solution outweigh the risks, hence a Marketing Authorisation has been granted.

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Module 1

Product Name	Latanoprost 0.005% w/v Eye Drops Solution
Type of Application	Article 10.3, Hybrid Application
Active Substance	Latanoprost
Form	Eye drops, solution 0.005%
Strength	0.005%
MA Holder	Orifarm Generics A/S Energivej 15 Odense S DK-5260 Denmark
RMS	UK
CMSs	Denmark, Germany, Finland, Norway and Sweden.
Procedure Number	UK/H/2237/001/DC
Timetable	End of Procedure: 20th October 2010

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Latanoprost 0.005% w/v Eye Drops, Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml of eye drops solution contains 50 micrograms of latanoprost (0.005% w/v).
Each drop contains 1.5 micrograms latanoprost.

Excipient: Contains 0.2 mg/ml (0.02% w/v) benzalkonium chloride.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Eye drops, solution
The solution is a clear colourless liquid.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Reduction of elevated intraocular pressure in patients with open angle glaucoma and ocular hypertension.

4.2 Posology and method of administration
Recommended dosage for adults (including the elderly):
Recommended therapy is one eye drop in the affected eye(s) once daily. Optimal effect is obtained if Latanoprost is administered in the evening.

The dosage of Latanoprost should not exceed once daily since it has been shown that more frequent administration decreases the intraocular pressure lowering effect.

If one dose is missed, treatment should continue with the next dose as normal.

As with any eye drops, to reduce possible systemic absorption, it is recommended that the lachrymal sac be compressed at the medial canthus (punctal occlusion) for one minute. This should be performed immediately following the instillation of each drop.

Contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart.
Paediatric population:
Safety and effectiveness in children has not been established. Therefore, Latanoprost is not recommended for use in children.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use
Latanoprost may gradually change eye colour by increasing the amount of brown pigment in the iris. Before treatment is instituted, patients should be informed of the possibility of a permanent change in eye colour. Unilateral treatment can result in permanent heterochromia.
This change in eye colour has predominantly been seen in patients with mixed coloured irides, i.e. blue-brown, grey-brown, yellow-brown and green-brown.

In studies with latanoprost, the onset of the change is usually within the first 8 months of treatment, rarely during the second or third year, and has not been seen after the fourth year of treatment. The rate of progression of iris pigmentation decreases with time and is stable for five years. The effect of increased pigmentation beyond five years has not been evaluated.

In an open 5-year latanoprost safety study, 33% of patients developed iris pigmentation (see section 4.8). The iris colour change is slight in the majority of cases and often not observed clinically. The incidence in patients with mixed colour irides ranged from 7 to 85%, with yellow-brown irides having the highest incidence. In patients with homogeneously blue eyes, no change has been observed and in patients with homogeneously grey, green or brown eyes, the change has only rarely been seen.

The colour change is due to increased melanin content in the stromal melanocytes of the iris and not to an increase in number of melanocytes. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. No further increase in brown iris pigment has been observed after discontinuation of treatment. It has not been associated with any symptom or pathological changes in clinical trials to date.

Neither naevi nor freckles of the iris have been affected by treatment. Accumulation of pigment in the trabecular meshwork or elsewhere in the anterior chamber has not been observed in clinical trials. Based on 5 years clinical experience, increased iris pigmentation has not been shown to have any negative clinical sequelae and Latanoprost can be continued if iris pigmentation ensues. However, patients should be monitored regularly and if the clinical situation warrants, Latanoprost treatment may be discontinued.

There is limited experience of Latanoprost in chronic angle closure glaucoma, open angle glaucoma of pseudophakic patients and in pigmentary glaucoma. There is no experience of Latanoprost in inflammatory and neovascular glaucoma, inflammatory ocular conditions, or congenital glaucoma. Latanoprost has no or little effect on the pupil, but there is no experience in acute attacks of closed angle glaucoma. Therefore, it is recommended that Latanoprost should be used with caution in these conditions until more experience is obtained.

There are limited study data on the use of Latanoprost during the peri-operative period of cataract surgery. Latanoprost should be used with caution in these patients.

Reports of macular oedema have occurred (see section 4.8) 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). Latanoprost 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 patients with known predisposing risk factors for iritis/uveitis, Latanoprost can be used with caution.

There is limited experience from patients with asthma, but some cases of exacerbation of asthma and/or dyspnoea were reported in post marketing experience. Asthmatic patients should therefore be treated with caution until there is sufficient experience, see also section 4.8.

Periorbital skin discolouration has been observed, the majority of reports being in Japanese patients. Experience to date shows that periorbital skin discolouration is not permanent and in some cases has reversed while continuing treatment with Latanoprost.

Latanoprost may gradually change eyelashes and vellus hair in the treated eye and surrounding areas; these changes include increased length, thickness, pigmentation, number of lashes or hairs and misdirected growth of eyelashes. Eyelash changes are reversible upon discontinuation of treatment.

Latanoprost contains benzalkonium chloride, which is commonly used as a preservative in ophthalmic products. Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy and may cause eye irritation. Close monitoring is required with frequent or prolonged use of Latanoprost in dry eye patients, or in conditions where the cornea is compromised.

Soft contact lenses may absorb benzalkonium chloride and become discoloured. Soft contact lenses should be removed before applying Latanoprost eye drops but may be reinserted after 15 minutes (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

There have been reports of paradoxical elevations in intraocular pressure following the concomitant ophthalmic administration of two prostaglandin analogues. Therefore, the use of two or more prostaglandins, prostaglandin analogues or prostaglandin derivatives is not recommended.

4.6 Pregnancy and lactation

Pregnancy

The safety of this medicinal product for use in human pregnancy has not been established. It has potential hazardous pharmacological effects with respect to the course of pregnancy, to the unborn or the neonate. Therefore, Latanoprost should not be used during pregnancy.

Lactation

Latanoprost and its metabolites may pass into breast milk and Latanoprost should therefore not be used in nursing women or breast feeding should be stopped.

4.7 Effects on ability to drive and use machines

Latanoprost has minor or moderate influence on the ability to drive and use machines. In common with other eye preparations, instillation of eye drops may cause transient blurring of vision.

4.8 Undesirable effects

The majority of adverse events relate to the ocular system. In an open 5-year latanoprost safety study, 33% of patients developed iris pigmentation (see section 4.4). Other ocular adverse events are generally transient and occur on dose administration.

Adverse events are categorized by frequency as follows: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,0000 to <1/1,000); very rare (<1/10,000).

Frequencies for events reported post-marketing are not known.

Eye Disorders:

Very common: Increased iris pigmentation; mild to moderate conjunctival hyperaemia eye irritation (burning grittiness, itching, stinging and foreign body sensation); eyelash and vellus hair changes (increased length, thickness, pigmentation and number) (vast majority of reports in Japanese population).

Common: transient punctate epithelial erosions, mostly without symptoms; blepharitis; eye pain.

Uncommon: Eyelid oedema: dry eye; keratitus; vision blurred; conjunctivitis.

Rare: Iritis/uveitis (the majority of reports in patients with concomitant predisposing factors); macular oedema; symptomatic corneal oedema and erosions; periorbital oedema; misdirected eyelashes sometimes resulting in eye irritation; extra row of cilia at the aperture of the meibomian glands (distichiasis).

Cardiac Disorders:

Very rare: Aggravation of angina in patients with pre-existing disease.

Respiratory, Thoracic and Mediastinal Disorders:

Rare: Asthma, asthma exacerbation and dyspnoea.

Skin and Subcutaneous Tissue Disorders:

Uncommon: Skin rash.

Rare: Localised skin reaction on the eyelids; darkening of the palpebral skin of the eyelids.

General Disorders and Administration Site Conditions:

Very rare: Chest pain.

There have been additional post-marketing spontaneous reports of the following:

Nervous System Disorders:

Headache, Dizziness.

Cardiac Disorders:
Palpitations.

Musculoskeletal and Connective Tissue Disorders:
Myalgia; Arthralgia.

4.9 Overdose

Apart from ocular irritation and conjunctival hyperaemia, no other ocular side effects are known if Latanoprost is overdosed.

If Latanoprost is accidentally ingested the following information may be useful: One bottle contains 125 micrograms latanoprost. More than 90% is metabolised during the first pass through the liver. Intravenous infusion of 3 micrograms/kg in healthy volunteers induced no symptoms, but a dose of 5.5-10 micrograms/kg caused nausea, abdominal pain, dizziness, fatigue, hot flushes and sweating. In monkeys, latanoprost has been infused intravenously in doses of up to 500 micrograms/kg without major effects on the cardiovascular system.

Intravenous administration of latanoprost in monkeys has been associated with transient bronchoconstriction. However, in patients with moderate bronchial asthma, bronchoconstriction was not induced by latanoprost when applied topically on the eyes in a dose of seven times the clinical dose of Latanoprost.

If overdosage with Latanoprost occurs, treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: (ATC code): S 01 E E 01

The active substance latanoprost, a prostaglandin $F_{2\alpha}$analogue, is a selective prostanoid FP receptor agonist which reduces the intraocular pressure by increasing the outflow of aqueous humour. Reduction of the intraocular pressure in man starts about three to four hours after administration and maximum effect is reached after eight to twelve hours. Pressure reduction is maintained for at least 24 hours.

Studies in animals and man indicate that the main mechanism of action is increased uveoscleral outflow, although some increase in outflow facility (decrease in outflow resistance) has been reported in man.

Pivotal studies have demonstrated that Latanoprost is effective as monotherapy. In addition, clinical trials investigating combination use have been performed. These include studies that show that latanoprost is effective in combination with beta-adrenergic antagonists (timolol).

Short-term (1 or 2 weeks) studies suggest that the effect of latanoprost is additive in combination with adrenergic agonists (dipivalyl epinephrine), oral carbonic anhydrase inhibitors (acetazolamide) and at least partly additive with cholinergic agonists (pilocarpine).

Clinical trials have shown that latanoprost has no significant effect on the production of aqueous humour. Latanoprost has not been found to have any effect on the blood-aqueous barrier.

Latanoprost has no or negligible effects on the intraocular blood circulation when used at the clinical dose and studied in monkeys. However, mild to moderate conjunctival or episcleral hyperaemia may occur during topical treatment.

Chronic treatment with latanoprost in monkey eyes, which had undergone extracapsular lens extraction, did not affect the retinal blood vessels as determined by fluorescein angiography.

Latanoprost has not induced fluorescein leakage in the posterior segment of pseudophakic human eyes during short-term treatment.

Latanoprost in clinical doses has not been found to have any significant pharmacological effects on the cardiovascular or respiratory system.

5.2 Pharmacokinetic properties

Latanoprost (mw 432.58) is an isopropyl ester prodrug which per se is inactive, but after hydrolysis to the acid of latanoprost becomes biologically active.

The prodrug is well absorbed through the cornea and all drug that enters the aqueous humour is hydrolysed during the passage through the cornea.

Studies in man indicate that the peak concentration in the aqueous humour is reached about two hours after topical administration. After topical application in monkeys, latanoprost is distributed primarily in the anterior segment, the conjunctivae and the eyelids. Only minute quantities of the drug reach the posterior segment.

There is practically no metabolism of the acid of latanoprost in the eye. The main metabolism occurs in the liver. The half life in plasma is 17 minutes in man. The main metabolites, the 1,2-dinor and 1,2,3,4-tetranor metabolites, exert no or only weak biological activity in animal studies and are excreted primarily in the urine.

5.3 Preclinical safety data

The ocular as well as systemic toxicity of latanoprost has been investigated in several animal species. Generally, latanoprost is well tolerated with a safety margin between clinical ocular dose and systemic toxicity of at least 1000 times. High doses of latanoprost, approximately 100 times the clinical dose/kg body weight, administered intravenously to unanaesthetised monkeys have been shown to increase the respiration rate probably reflecting bronchoconstriction of short duration. In animal studies, latanoprost has not been found to have sensitising properties.

In the eye, no toxic effects have been detected with doses of up to 100 micrograms/eye/day in rabbits or monkeys (clinical dose is approximately 1.5 micrograms/eye/day). In monkeys, however, latanoprost has been shown to induce increased pigmentation of the iris.

The mechanism of increased pigmentation seems to be stimulation of melanin production in melanocytes of the iris with no proliferative changes observed. The change in iris colour may be permanent.

In chronic ocular toxicity studies, administration of latanoprost 6 micrograms/eye/day has also been shown to induce increased palpebral fissure. This effect is reversible and occurs at doses above the clinical dose level. The effect has not been seen in humans.

Latanoprost was found negative in reverse mutation tests in bacteria, gene mutation in mouse lymphoma and mouse micronucleus test. Chromosome aberrations were observed in vitro with human lymphocytes. Similar effects were observed with prostaglandin $F_{2\alpha}$, a naturally occurring prostaglandin, which indicates that this is a class effect.

Additional mutagenicity studies on in vitro/in vivo unscheduled DNA synthesis in rats were negative and indicate that latanoprost does not have mutagenic potency. Carcinogenicity studies in mice and rats were negative.

Latanoprost has not been found to have any effect on male or female fertility in animal studies. In the embryotoxicity study in rats, no embryotoxicity was observed at intravenous doses (5, 50 and 250 micrograms/kg/day) of latanoprost. However, latanoprost induced embryolethal effects in rabbits at doses of 5 micrograms/kg/day and above.
The dose of 5 micrograms/kg/day (approximately 100 times the clinical dose) caused significant embryofetal toxicity characterised by increased incidence of late resorption and abortion and by reduced fetal weight.

No teratogenic potential has been detected.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Disodium phosphate anhydrous
Sodium dihydrogen phosphate monohydrate

Benzalkonium chloride
Water for injections

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Shelf life: 24 months
Shelf life after first opening: 4 weeks

6.4 Special precautions for storage
Keep the bottle in the outer carton in order to protect from light.
Store in a refrigerator (2°C – 8°C).
After first opening: Do not store above 25°C and use within four weeks.

6.5 Nature and contents of container
Dropper container: 5 ml white translucent LDPE container containing 2.5 ml fill volume
Dropper applicator: White translucent LDPE dropper
Cap: White opaque HDPE cap

Pack sizes: 1 x 2.5 ml, 3 x 2.5 ml or 6 x 2.5 ml bottles

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Orifarm Generics A/S
Energivej 15, 5260 Odense S
Denmark

8 MARKETING AUTHORISATION NUMBER(S)
PL 20254/0038

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
16/12/2010

10 DATE OF REVISION OF THE TEXT
16/12/2010

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Latanoprost 0.005% w/v Eye Drops, Solution

Latanoprost

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. 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 pharmacist.

In this leaflet:

1. What Latanoprost Eye Drops are and what they are used for

Latanoprost belongs to a group of medicines called prostaglandins. It works by increasing the natural outflow of fluid from inside the eye into the bloodstream.

Latanoprost eye drops are used to treat conditions known as **open angle glaucoma** and **ocular hypertension**. Both of these conditions are linked with an increase in the pressure within your eye, eventually affecting your eye sight.

2. Before you use Latanoprost Eye Drops

Latanoprost eye drops can be used in adult men and women (including the elderly) but is not recommended for use if you are less than 18 years of age.

Do not use Latanoprost eye drops if:
- you are allergic (hypersensitive) to latanoprost or to any of the other ingredients in this medicine (listed in Section 6)

Do not use this medicine if the above applies to you. If you are not sure, talk to your doctor or pharmacist before using Latanoprost eye drops.

Take special care with Latanoprost eye drops
Check with your doctor or pharmacist before using your medicine if:
- you have a condition known as chronic angle closure glaucoma, neovascular glaucoma or congenital glaucoma.
- you are about to have or have had eye surgery (including cataract surgery).

- you have an eye in which a lens is not present or is partially or completely opaque.
- you have a condition known as diabetic retinopathy or retinal vein occlusion.
- you suffer from eye problems (such eye pain, irritation or inflammation, blurred vision)
- you have ever been treated for eye problems known as iritis and uveitis or know you suffer from dry eyes.
- you have severe asthma or your asthma is not well controlled.
- you wear contact lenses. You can still use Latanoprost eye drops, but follow the instructions for contact lens wearers in Section 3 'Using the medicine'.

If any of the above applies to you (or you are not sure), please talk to your doctor or pharmacist before using Latanoprost eye drops.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you get without a prescription.

- Tell your doctor or pharmacist if you are using other medicines for your eyes.

If this applies to you (or you are not sure), talk to your doctor or pharmacist before using Latanoprost eye drops.

Pregnancy and breast-feeding
Do not use Latanoprost eye drops if:

- you are pregnant. Tell your doctor immediately if you are pregnant, think you are pregnant, or are planning to become pregnant.
- you are breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
You may find it difficult to see when you first add your eye drops. Do not drive or use any tools or machines until you know how Latanoprost eye drops affect you. Ask your doctor or pharmacist if you are not sure.

Important information about some of the ingredients of Latanoprost eye drops
Latanoprost eye drops contain benzalkonium chloride. This may irritate your eyes. Benzalkonium chloride is also known to discolour soft contact lenses. You should avoid contact with soft contact lenses. Remove your contact lenses before using Latanoprost eye drops and wait 15 minutes before you put your contact lenses back in.

3. How to use Latanoprost Eye Drops

Always use Latanoprost eye dropsexactly as your doctor has told you.
You should check with your doctor or pharmacist if you are not sure.

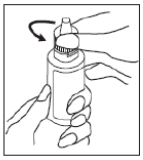
How much to use
The usual dose is one drop each day in the affected eye(s).The best time to do this is in the evening.
Do not use Latanoprost eye drops more than once a day, because the effectiveness of the treatment can be reduced if you administer it more often.

Using the medicine

Contact lens wearers
If you wear contact lenses, take them out before you use Latanoprost eye drops. Wait 15 minutes before you put your contact lens back in after using Latanoprost eye drops.

Instructions for use
- If you are using any other eye drops, wait 5 minutes before using them after Latanoprost eye drops.

1. Wash your hands before using Latanoprost eye drops.
2. Twist off the cap as shown below:



3. Use your finger to gently pull down the lower eyelid of your affected eye.
4. Place the tip of the container close to your eye taking care not to touch your eye.
5. Squeeze the container gently so that only one drop goes into your eye, then let go of your eyelid.

6. Press a finger against the corner of the affected eye by the nose. Hold for 1 minute whilst keeping the eye closed.
7. Repeat steps 3 to 6 for the other eye if your doctor has told you to do this.
8. Place the cap back on the bottle.

If you use more Latanoprost eye drops than you should
If you put too many drops into your eye, you may experience some minor irritation in your eye and your eye may water and turn red, this should pass, but if you are worried contact your doctor for advice.
Contact your doctor as soon as possible if you swallow Latanoprost eye drops accidentally.

If you forget to use Latanoprost eye drops
Carry on with the usual dosage at the usual time. Do not use a double dose to make up for the dose you have forgotten. If you are unsure about anything talk to your doctor or pharmacist.

If you stop using Latanoprost eye drops
You should speak to your doctor if you want to stop using Latanoprost eye drops.

If you have any further questions on using this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Latanoprost eye drops can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

Very common (affects more than 1 in 10 people)
- gradual change in eye colour by increasing the amount of brown pigment in the coloured part of the eye known as the iris. If you have mixed-colour eyes (blue-brown, grey-brown, yellow-brown or green-brown) you are more likely to see this change than if you have eyes of one colour (blue, grey, green or brown eyes). Any changes in your eye colour may take years to develop although it is normally seen within 8 months of treatment. The colour change may be permanent and may be more noticeable if you use Latanoprost eye drops in only one eye. There appears to be no problems associated with the change in eye colour. The eye colour change does not continue after Latanoprost eye drops treatment is stopped.
- redness of the eye
- eye irritation (a feeling of burning, grittiness, itching, stinging or the sensation of a foreign body in the eye).
- a gradual change in your eye lashes. A gradual change to eyelashes of the treated eye and the fine hairs around the treated eye, seen mostly in people of Japanese origin. These changes involve an increase of the colour (darkening), length, thickness and number of your eye lashes.

Common (affects less than 1 in 10 people)
- irritation or disruption to the surface of the eye, eyelid inflammation (blepharitis) and eye pain.

Uncommon (affects less than 1 in 100 people)
- eyelid swelling, dryness of the eye, inflammation or irritation of the surface of the eye (keratitis), blurred vision and conjunctivitis.
- skin rash.

Rare (affects less than 1 in 1,000 people)
- inflammation of the iris, the coloured part of the eye (iritis/uveitis); swelling of the retina (macular oedema), symptoms of swelling or scratching/damage to the surface of the eye, swelling around the eye (periorbital oedema), misdirected eyelashes or an extra row of eyelashes.
- skin reactions on the eye lids, darkening of the skin of the eyelids.
- asthma, worsening of asthma, shortness of breath (dyspnoea).

Very rare (affects less than 1 in 10,000 people)
- Worsening of angina in patients who also have heart disease. Chest pain.

It is not known how many people will get the following:
- headaches or feeling dizzy
- palpitations
- pains in your muscles or joints

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

5. How to store Latanoprost Eye Drops

- Keep out of the reach and sight of children.
- Do not use Latanoprost eye drops after the expiry date which is stated on the carton and container after EXP. The expiry date refers to the last day of that month.
- Keep the bottle in the outer carton in order to protect from light.
- Store in a refrigerator (2°C – 8°C).
- After first opening: Do not store above 25°C and use within four weeks.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Further information

What Latanoprost eye drops contain
- The active substance is latanoprost.
- 1 ml of eye drops solution contains 50 micrograms of latanoprost (0.005% w/v).
- Each drop contains 1.5 micrograms latanoprost.
- The other ingredients are sodium chloride, disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, benzalkonium chloride and water for injections.

What Latanoprost eye drops look*s* like and contents of the pack
- The drops are a clear colourless solution.
- The drops are available in a 5 ml bottle, containing 2.5 ml eye drop solution.
- The 5 ml bottles are available in boxes of 1, 3 or 6 bottles.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
[To be completed nationally]

Manufacturer:
[To be completed nationally]

<*Distributor:* [To be completed nationally]>

This leaflet was last approved in {MM/YYYY}.

Module 4
Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

Latanoprost 0.005% w/v Eye Drops, Solution
Latanoprost

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of eye drops solution contains 50 micrograms of latanoprost (0.005% w/v).
Each drop contains 1.5 micrograms latanoprost.

3. LIST OF EXCIPIENTS

Contains benzalkonium chloride. See package leaflet for further information.

Also contains: sodium chloride, disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

2.5 ml
Eye drops, solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For ocular use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: mm/yyyy or similar

<Opening date:>

9. SPECIAL STORAGE CONDITIONS

Keep the bottle in the outer carton in order to protect from light.
Store in a refrigerator (2°C – 8°C).
After first opening: Do not store above 25°C and use within four weeks.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

<*Distributor:* [To be completed nationally]>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot.:

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LDPE Container

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Latanoprost Apotex 0.005% w/v Eye Drops, Solution
Latanoprost

2. METHOD OF ADMINISTRATION

For ocular use.

3. EXPIRY DATE

EXP: mm/yyyy or similar

4. BATCH NUMBER

BN:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 ml

6. OTHER

Keep the bottle in the outer carton in order to protect from light.
Store in a refrigerator (2°C – 8°C).
After first opening: Do not store above 25°C and use within four weeks.

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the application for Latanoprost 0.005% w/v Eye Drops, Solution, in the treatment of reduction of elevated intraocular pressure in patients with open angle glaucoma and ocular hypertension, could be approved.

This application was submitted under a decentralised procedure (DCP), according to Article 10.3 of Directive 2001/83 EC, as amended, hybrid application. The reference product to which this application refers is Xalatan 0.005% Eye drops, (PL 00032/0220) licensed to Pharmacia Limited, UK, on the 16th December 1996. The reference product has been authorised in the EEA for more than 10 years.

With UK as the RMS in this Decentralised Procedure (UK/H/2237/001/DC), Orifarm Generics A/S applied for the Marketing Authorisation for Latanoprost 0.005% w/v Eye Drops, Solution in Denmark, Germany, Finland, Norway and Sweden.

Latanoprost is a synthetic analogue of dinoprost (prostaglandin F2α). It reduces IOP by increasing uveoscleral outflow without affecting aqueous flow or the permeability of the blood-aqueous barrier. This mechanism is therefore different to other antiglaucoma therapies. Although the exact mechanisms are not clear, prostaglandins open the uveoscleral pathway in the ciliary muscle by reducing the extracellular matrix in the spaces among ciliary muscle fibres. Relaxation of the ciliary muscle may also promote increased uveoscleral outflow.

No new preclinical studies were conducted, which is acceptable given that the application is a hybrid application based on originator product that has been licensed for over 10 years. The clinical data submitted in support of this application include the data from one therapeutic equivalence study (Study code: APT 01) and a summary of data from published literature on the safety and efficacy of latanoprost eye drops.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification has been provided for non-submission of a Risk Management Plan.

All member states agreed to grant respective licence for the above product at the end of procedure (Day 210 – 20th October 2010). After a subsequent national phase, the UK granted a licence for this product on 16th December 2010 (PL 20254/0038).

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Latanoprost 0.005% w/v Eye Drops Solution
Name(s) of the active substance(s) (USAN)	Latanoprost
Pharmacotherapeutic classification (ATC code)	S 01 E E 01
Pharmaceutical form and strength(s)	Eye drops, solution 0.005%
Reference numbers for the Decentralised Procedure	UK/H/2237/001/DC
Reference Member State	United Kingdom
Concerned Member States	Denmark, Germany, Finland, Norway and Sweden.
Marketing Authorisation Number(s)	PL 20254/0038
Name and address of the authorisation holder	Orifarm Generics A/S Energivej 15 Odense S DK-5260 Denmark

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

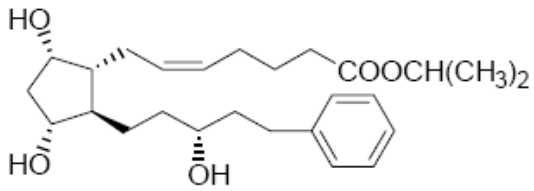
INN: Latanoprost

Chemical Names: Isopropyl-(*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(3*R*)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate

[1*R*-[1α(*Z*),2β(*R*),3α, 5α]]-7-[3,5-Dihydroxy-2-(3-hydroxy-5-phenylpentyl) cyclopentyl]-5-heptenoic acid]-methylethyl ester

13,14-Dihydro-17-phenyl-18,19,20-trinor-PGF2α-isopropyl ester

Structure:



Molecular formula: $C_{26}H_{40}O_5$

Molecular weight: 432.58

Physical form: Latanoprost is a clear to pale yellowish viscous oil, practically insoluble in water and freely soluble in alcohols, chloroform, and acetone.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period for active latanoprost when stored in the proposed packaging.

DRUG PRODUCT

Other Ingredients

Other ingredients consist of the pharmaceutical excipients sodium chloride, disodium phosphate anhydrous, sodium dihydrogen phosphate monohydrate, benzalkonium chloride and water for injections.

All excipients comply with the European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for these excipients.

The above excipients do not contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development
The objective of the pharmaceutical development programme was to obtain stable product containing latanoprost that could be considered a hybrid product of Xalatan 0.005% w/v Eye Drops, Solution (PL 00032/0220) licensed to Pharmacia Limited, UK, on the 16th December 1996.

Suitable pharmaceutical development data have been provided for this application.

Manufacture
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished products. Process validation has been carried out on batches of the product. The results are satisfactory.

Finished Product Specifications
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The finished product is packaged in translucent LDPE container with LDPE dropper and HDPE cap

Pack size: 1 x 2.5 ml, 3 x 2.5 ml or 6 x 2.5 ml bottles

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidelines.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 24 months for unopened container has been set, with storage conditions “Keep the bottle in the outer carton in order to protect from light” and “Store in a refrigerator (2°C – 8°C)”. After first opening a shelf- life 4 weeks with storage condition of “Do not store above 25°C and use within four weeks” has been set. These are satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SPC, PIL and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive

2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) Forms
The MAA form is pharmaceutically satisfactory.

Expert Report
A pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical point of view.

III.2 PRE-CLINICAL ASPECTS
PHARMACODYNAMICS, PHARMACOKINETICS, TOXICOLOGY

The pharmacological, pharmacokinetic and toxicological properties of Latanoprost are well-known.

No new preclinical data have been supplied with this application and none are required for applications of this type. The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of the environmental risk assessment.

There are no objections to the approval of this product from a pre-clinical point of view.

III.3 CLINICAL ASPECTS

Pharmacokinetics
No new data have been submitted and none are required for applications of this type.

This application is for generic medicinal product of Xalatan 0.005% Eye drops, (PL 00032/0220), which was originally granted to Pharmacia Limited, UK, on the 16th December 1996. The use of the reference product is well-established in the UK.

Pharmacodynamics
No new data have been submitted and none are required for applications of this type.

Clinical efficacy
Introduction
The therapeutic equivalence of the applicant's product, *Latanoprost 0.005% w/v Eye drops solution*, to the reference product, Laxatan 0.005% (Pharmacia Limited), was assessed in a comparative, randomised, investigator-blind, two-way crossover efficacy study against Xalatan® (Pharmacia Limited) in open angle glaucoma and ocular hypertensive patients (APT01). This study has been discussed below.
The applicant has also provided a bibliographic summary of the efficacy data on latanoprost ophthalmic solution in the Clinical Overview.

Main study

Study title: **Comparative, randomised, investigator-blind, two-way crossover efficacy study of Latanoprost Ophthalmic Solution (Apotex) and Xalatan® (Pharmacia Limited) in open angle glaucoma and ocular hypertensive patients (study code: APT01)**

This therapeutic equivalence study was conducted on behalf of Apotex Inc. by Appletree AG, Winterthur, Switzerland to compare the efficacy (in terms of intraocular pressure lowering) and tolerability of the Apotex Latanoprost 0.005% Ophthalmic Solution (test) and Xalatan 0.005% (Pharmacia Limited, reference) in patients with either open angle glaucoma or ocular hypertension.
The study was designed as a randomised, Phase III, investigator-blind, two-way crossover study conducted in seven study sites in Romania and Czech Republic. Patients selected for the study had to be aged 18-75 years, of either sex, with elevated IOP and open angles in at least one eye (>22 to <34 mm Hg at -12, -8, -4 and 0 hours on day 1 pretreatment) and not currently on any IOP-lowering or other topical ophthalmic medication other than artificial tears. In addition, there was to have been no ocular trauma, surgery, inflammation, infection or corneal foreign body within the previous three months to study start, and no clinically relevant or progressive retinal disease present. The patient was not to have received any ocular glucocorticoid medication during this period. Other conditions for eligibility included no concomitant use of any medication that may have increased adrenergic activity (e.g amitriptyline) or other systemic medication likely to have affected IOP within the previous 30 days, or during the study (e.g. β blockers, calcium antagonists, ACE inhibitors, prostaglandins). Patients could be contact lens wearers but these were to be removed for a specified period around the time of administration of the study medications. Patient general health was required to be good and not interfere with study participation and females of childbearing potential were eligible provided the usual safeguards for prevention of conception were in place.

1. Although a double-blind design would be preferable, the investigator-blind approach has also been used in trials in this area. Given a level of operator dependency in measuring IOP using Goldman method, it was important that the operator remained blind to the treatment.
2. The choice of the target population corresponds to the approved indications of latanoprost and is appropriate.
3. Adding a placebo arm to the trial could have provided an internal means to demonstrate the assay sensitivity. Adequate assay sensitivity in this case may be deduced from historical evidence of sensitivity to Xalatan effects. Historical evidence of sensitivity to Xalatan efficacy in head to head trials against other IOP lowering drugs is well-documented and has been adequately covered in the Clinical Overview. According to ***ICH Topic E 10, Choice of Control Group in Clinical Trials (CPMP/ICH/364/96)*** this is acceptable.

Should both eyes of a patient have met the eligibility criteria for raised mean diurnal IOP, the nomination of the study eye was by means of a second randomisation if IOP values were the same in both eyes, otherwise the eye with the higher IOP was selected as the study eye. Patient exclusion criteria comprised a distance Snellen visual acuity of <20/100 in either eye and other ocular pathology likely to have interfered with the study results. Full details of patient inclusion and exclusion criteria are to be found within the clinical study protocol and final study report.
The study was conducted in accordance with the ICH guidelines on Good Clinical Practice and the Declaration of Helsinki and the protocol was approved by the relevant regulatory

authority of the countries concerned as well as an independent ethics committee prior to study start. All patients gave fully informed consent to take part.
Following the screening visit, patients underwent a six week washout period if they had been treated with a prostaglandin analogue, or a four week washout if pre-treated with any other IOP-lowering medication, otherwise no washout period was required if the patient was treatment-naïve. They then received one of the two study treatments (either test or reference) in randomised order, for 28 days, followed by a six week washout period, then the alternative study treatment for a further 28 days. The study medications were administered as one drop into the affected eye(s) once daily in the evening every day between 2000 and 2200 hours.

The washout period prior to period one is adequate. Individual efficacy response data show that the IOP at the start of period 2 had returned to the baseline. The washout in between the two treatment periods is considered adequate.

The study drugs were administered by the patient at home, except for Days 1, 14 and 28 of each treatment period, when the Investigational Product was instilled by the responsible personnel of the clinical study centre. Follow-up telephone contact was made on day 7 or 8 to assess how patients were faring and to assess compliance. Patients recorded the time of study drug administration and any adverse events on diary cards. Follow-up clinic visits were made on days 14, 28 and 29 of both study periods. After either washout period, the patients reported to the clinic at least 12 hours before administration of the drug on Day 1. IOP was measured using a Goldmann applanation tonometer at -12, -8, -4, and -0 hours prior to dosing. At the Visits 2 and 6 (Day 14 of each period) the IOP was measured pre-dose in the evenings. For the final IOP diurnal curve on Day 29 the Investigational Product was administered by the assigned site staff in the evening of Day 28 in order to guarantee that patients were treated before the diurnal curve. At the last visit of each period (V4 and V8) patients returned to the clinic a maximum of 12 hours after the last dosing of the Investigational Product and had IOP measured at 12, 16, 20, and 24 hours after the last dosing. The mean diurnal IOP was calculated as the arithmetic mean of the four determinations. Safety was assessed by evaluating ocular discomfort, conjunctival hyperaemia, vital signs (blood pressure, heart rate) and adverse events on Days 14 and 29 in each study period.

1. Goldmann tonometry is considered to be the gold standard in tonometry as it is the most widely accepted method of determining approximate intraocular pressure.
2. The study medications were instilled in the evening as recommended in the reference product's SPC.

3. IOP measurements at 4 time points (-12, -8, -4 and 0 hours prior to dosing) should in principle cover the diurnal variation of IOP adequately. Several authors have assessed from 3 – 6 measurements in determining diurnal IOP. Therefore, 4 measurements at the stated time points are considered adequate.

The primary endpoint of the study was the difference between the investigational products with respect to change in mean diurnal IOP in the study eye(s) between day 29 (post-dose of day 28) and baseline (pre-dose day 1).

Mean diurnal IOP as the primary endpoint has previously been used in comparative clinical trials with latanoprost and is adequately validated.

Therapeutic equivalence of the two latanoprost products was declared if the 95% confidence intervals (CI) of the difference in change of mean diurnal IOP between baseline and day 29 between test and reference products was less than ±1.5 mm Hg. Secondary endpoints included the difference between the investigational products with respect to the proportion of patients with a >20% reduction of diurnal IOP from baseline and three safety parameters : difference between products with regard to ocular discomfort and conjunctival hyperaemia at baseline compared with days 14 and 28 and with regard to general safety, as assessed by adverse events. Both ocular discomfort and conjunctival hyperaemia were assessed on 5-point categorical scales which are described in the protocol.
A sample size of 48 patients was calculated to provide a 90% power to detect a 95% CI difference in change of IOP between test and reference products of ±1.5 mm Hg, assuming an intra-patient SD of 2.25 mm Hg. Assuming a dropout / withdrawal rate of 20%, then 60 patients were required for recruitment into the study. The primary endpoint was calculated on both intent-to-treat (ITT) and per protocol (PP) basis. The ITT population was defined as all patients who completed the first treatment period and received at least one dose of the second treatment. The PP population was defined as all patients who completed the study in its entirety without any major protocol violations. The safety population included all patients who received at least one dose of the study medication.

An equivalence margin of ± 1.5 mmHg is acceptable for mean diurnal IOP and is consistent with the published literature.

Disposition of Patients

A total of 71 patients were screened, of whom 59 (mean age 55.3 + 12.5 yr, range 24-75 yr) were enrolled and 56 completed the study (Intention to treat, ITT, population). The per protocol (PP) population comprised 52 patients. There were slightly more females than males (57.6% vs 42.4%). A total of 61% had open angle glaucoma, the remainder had ocular hypertension. Disposition of patients is summarised in the following table:

Disposition of patients

	Statistic	A: Test/Ref N = 27	B: Ref/Test N = 32	Total N = 71
Number of Patients in the APP Population				
	% (n/N)			100% (71/71)
Number of Patients in the SAF Population				
	% (n/N)	100% (27/27)	100% (32/32)	83.1% (59/71)
Number of Patients in the ITT Population				
	% (n/N)	100% (27/27)	90.6% (29/32)	78.9% (56/71)
Number of Patients in the PP Population				
	% (n/N)	88.9% (24/27)	87.5% (28/32)	73.2% (52/71)

Protocol Deviations:

Major protocol violations are summarised in the following table:

Patient number	ITT	PP	Reason for exclusion from PP / PP and ITT
107	Yes	No	Study eye IOP below 22 mmHg at Visit 5
110	Yes	No	Study eye IOP below 22 mmHg at Visit 5
114	Yes	No	Patient started taking Metoprolol during the study period, a concomitant medication interfering with the IOP.
115	Yes	No	The patient stopped taking the IMP from Day 21 to day 24 due to stinging and tearing (AE).
118	No	No	The patient quit the study due to AE after the Baseline Visit.
505	No	No	The patient quit the study due to an AE before Visit 2.
705	No	No	The patient did not come to the Visit 5, lost-to follow-up

The listed major protocol violations are unlikely to have a significant impact on the study results.

Baseline demographics:

Baseline demographic characteristics of the study participants are summarised in the following table:

	Statistic	Screening Failure N = 12	A: Test/Ref N = 27	B: Ref/Test N = 32	A+B N = 59
Gender					
Male	% (n/N)	58.3% (7/12)	40.7% (11/27)	43.8% (14/32)	42.4% (25/59)
Female	% (n/N)	41.7% (5/12)	59.3% (16/27)	56.3% (18/32)	57.6% (34/59)
Age (years)					
	n	12	27	32	59
	Mean (SD)	52.6 (9.42)	55.1 (12.40)	55.5 (12.80)	55.3 (12.51)
	Median (range)	53.5 (37, 66)	56.0 (25, 71)	57.0 (24, 75)	56.0 (24, 75)
Ethnicity					
Caucasian	% (n/N)	100% (12/12)	100% (27/27)	100% (32/32)	100% (59/59)

There were slightly more women than men (57.6% women and 42.4% men). The mean age was 55.3 years. Minimum age was 24 and maximum age was 75. All patients were Caucasian.

Demographics and other baseline characteristics are in accordance with the protocol.

Results

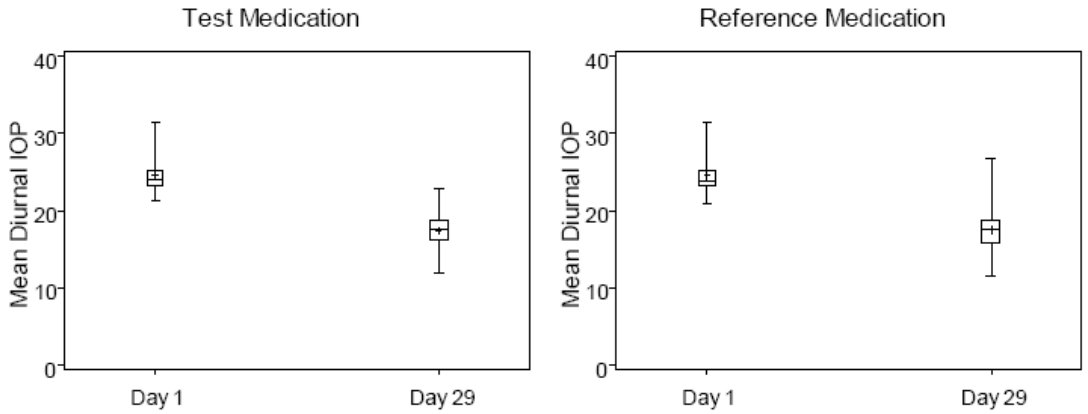
Primary Endpoint:

The following table presents descriptive statistics of the mean diurnal IOP measurement for Day 1 and Day 29 by the current treatment together with the change in mean diurnal IOP between day 1 and day 29 for the PP population, followed by another table presenting the same information for the ITT population:

		Test Product		
	Statistic	**Day 1 N = 52**	**Day 29 N = 52**	**Change N = 52**
Intraocular Pressure				
	n	52	52	52
	Mean (SD)	24.4 (1.82)	17.5 (2.21)	-6.9 (2.16)
	Median (range)	24.0 (22, 32)	17.7 (12, 23)	-6.5 (-13, -4)
		Reference Product		
	Statistic	**Day 1 N = 52**	**Day 29 N = 52**	**Change N = 52**
Intraocular Pressure				
	n	52	52	52
	Mean (SD)	24.5 (2.16)	17.6 (2.64)	-6.9 (2.07)
	Median (range)	23.9 (22, 32)	17.8 (12, 27)	-6.8 (-12, -3)

		Test Product		
	Statistic	**N = 52**	**Day 29 N = 52**	**Change N = 52**
Intraocular Pressure				
	n	56	56	56
	Mean (SD)	24.4 (1.97)	17.4 (2.23)	-7.0 (2.26)
	Median (range)	24.0 (21, 32)	17.5 (12, 23)	-6.5 (-13, -4)
		Reference Product		
	Statistic	**Day 1 N = 52**	**Day 29 N = 52**	**Change N = 52**
Intraocular Pressure				
	n	56	56	56
	Mean (SD)	24.4 (2.21)	17.5 (2.58)	-6.9 (2.08)
	Median (range)	23.8 (21, 32)	17.5 (12, 27)	-6.8 (-12, -3)

Box plots of mean diurnal IOP in the study eye by visit and treatment – ITT population – are presented below:



Analysis of change in mean diurnal IOP: least square means – PP population – is summarised in the following table:

		Test Medication	Reference Medication	Difference	P-value for the Difference
Mean Diurnal IOP (mmHg)					
	Estimate (SE)	-7.0 (0.28)	-6.9 (0.28)	-0.1 (0.30)	0.677
	95% CI	[-7.55, -6.43]	[-7.45, -6.32]	[-0.61, 0.40]	

Analysis of change in mean diurnal IOP: least square means – ITT population – is summarised in the following table:

		Test Medication	Reference Medication	Difference	P-value for the Difference
Mean Diurnal IOP (mmHg)					
	Estimate (SE)	-7.1 (0.27)	-6.9 (0.27)	-0.1 (0.25)	0.636
	95% CI	[-7.59, -6.52]	[-7.47, -6.40]	[-0.62, 0.38]	

A sample size of 48 evaluable patients was calculated to provide a 90% power that the 95% confidence interval of the difference in change of mean diurnal IOP from baseline between the two products would be within 1.5 mmHg, assuming an intra-patient standard deviation of 2.25 mmHg and no real difference between the two products. Assuming a drop-out rate of 20%, 60 patients were to be recruited for the study.
A total of 71 patients were screened, of whom 59 (mean age 55.3 + 12.5 yr, range 24-75 yr) were enrolled and 56 completed the study (Intention to treat, ITT, population). The per protocol (PP) population comprised 52 patients. A total of 61% had open angle glaucoma, the remainder had ocular hypertension.
In the PP population mean (+SD) IOP decreased from 24.4 + 1.8 mm Hg at baseline to 17.5 + 2.2 mm Hg at day 29 in the test group (-6.9% change) and from 24.5 + 2.2 mm Hg to 17.6 + 2.6 mm Hg in the reference group (-6.9% change). ITT and PP analyses are consistent. 95% confidence interval of the difference in change of mean diurnal IOP from day 1 to day 29 between the Test Product and the Reference Product is (-0.61 , 0.40) for the pre-protocol population, well within the pre-specified limits of ±1.5 mmHg.
The mean baseline was 24.5, and both groups had a mean change of -7.0, or 28.5%. This is consistent with the expected change of the reference of between 20% and 35% and provides some evidence that a sufficient treatment benefit has been established.

Secondary endpoints:
For the secondary endpoint of patient responders (>20% reduction in mean diurnal IOP) there were 43 patients who responded to both test and reference products, five who responded to the test product but not the reference product, and three who responded to the reference, but not the test, product (one patient responded to neither). By McNemar's (p=0.727) and Maitland Gart (p=0.464) statistical tests there was no statistically significant association between period response and treatment sequence, thereby indicating a lack of statistically significant difference in treatment success (i.e. >20% reduction in IOP) between the two treatments.
Regarding safety and tolerability, based on a 5-point categorical scale, similar proportions of patients (approximately 90-95%) experienced ocular discomfort (mostly of mild or moderate severity) throughout the study in both groups. These proportions were not significantly different. Conjunctival hyperaemia was experienced more frequently with the reference product on days 14 and 28 of treatment and the differences with the test product were significant on these occasions (p=0.036 and p=0.023, respectively). However, these differences in conjunctival hyperaemia were marginal and over 90% of patients in both groups tolerated the study treatments well or very well. The observed differences in mostly mild hyperaemia may well have been due to chance given the identical formulation (including excipients) in the test and reference latanoprost products.

More patients experienced adverse events in period 1 (27.1%) than in period 2 (10.2%). This was as a result of assigning adverse events occurring in the washout period to period 1. The majority of adverse events were ocular in nature. Although slightly more patients experienced an adverse event that started when they were using the reference product (37.3%) than when they were using the test product (25.0%) these differences were not statistically significant. There were no serious adverse events occurring in the study. Only minor, clinically insignificant changes in vital signs (blood pressure, heart rate) were observed with either treatment.

Both the test and the reference products were well-tolerated. Small differences in conjunctival hyperaemia favoured the test product.

Overview of Efficacy – Literature Review

Comparison of latanoprost 0.001% and 0.005%

A small double-blind, crossover study in 24 patients with glaucoma or ocular hypertension evaluated the IOP-lowering effects of both 0.001% and 0.005% latanoprost given once daily (od) for four weeks. Significant IOP reductions from baseline were seen with both treatments: 7.6 + 3.4 mm Hg with 0.001% latanoprost and 9.6 + 3.3 mm Hg with 0.005% latanoprost (p<0.001 in favour of the 0.005% solution). Both treatment groups showed a better response (by 1.1 mm Hg) during the second treatment period, but this was unlikely to be due to a carry-over effect because of the absence of a washout period between the two study periods, since the ANOVA test of carry-over effect was not significant (p=0.46) and it would be unlikely that a carry-over effect would be apparent from the lower concentration to the higher. Other studies have confirmed that a single drop of latanoprost 0.005% solution (about 1.5 μg) once daily is the most effective dosage regimen and this dosage has been used in most reported studies.

Latanoprost versus timolol as monotherapies

There have been a number of publications comparing latanoprost 0.005% and timolol 0.5% as ophthalmic solutions for the treatment of glaucoma or ocular hypertension. Most large 9 double-blind trials have shown IOP reductions due to latanoprost of 27-35% and from timolol of 19-33% over 3-6 months of treatment. Latanoprost also appears to have a more

consistent 24 hour effect than timolol. One meta analysis of 11 such randomised controlled trials of the two agents in 1256 patients evaluated percentage IOP reduction, relative risk, risk difference, and number needed to harm (NNH) for adverse effects and reductions in systemic blood pressure and heart rate as side effects, all as main outcome measures Treatment periods ranged between one week and 12 months. All studies in the analysis were consistent in showing an efficacy advantage for latanoprost over timolol, and the overall mean percentage reduction (SE) in IOP from baseline was 30.2 (2.3) for latanoprost and 26.9 (3.4) for timolol at three months. The difference in IOP reduction between treatments was 5.0 (95% CI 2.8, 7.3) in favour of latanoprost, although it caused more iris pigmentation than timolol (relative risk 8.01, 95% CI 1.87, 34.3), with the two year risk reaching 18%. Conjunctival hyperaemia was also more common with latanoprost (relative risk 2.2, 95% CI 1.33, 3.64), but timolol caused a significant reduction in heart rate (4/min, 95% CI 2, 6). Evening dosing of latanoprost was associated with a pooled difference of 5.1% (33.2% versus 28.1%, p=0.006) compared with morning dosing. Although evening dosing was marginally better than the twice daily regimen, this resulted only in numerically, but not statistically, different IOP reductions (5.5%, p=0.17). Latanoprost also reduces IOP further than timolol 0.5% over 2-12 week periods in patients with angle-closure glaucoma. Although the primary treatment for this condition is peripheral iridotomy, many patients continue to have elevated IOP following surgery and are therefore candidates for topical therapy while awaiting surgical iridectomy or trabeculectomy. The degree of angle closure did not affect the extent of IOP reduction in the comparative trials of latanoprost versus timolol monotherapies. Other small studies have demonstrated that latanoprost has comparable efficacy to timolol in patients with normal tension and steroid-induced glaucoma over periods of 3 weeks – 4 months, and is also more effective than timolol in patients with pigmentary glaucoma after 12 months' therapy.

Latanoprost versus dorzolamide/timolol combination

Comparisons of latanoprost 0.005% od with the dorzolamide 2% / timolol 0.5% fixed combination bd in randomised controlled trials have generally shown equivalent efficacy with regards to reductions in mean daytime diurnal IOP. A post hoc analysis of two pooled three month, parallel group, double-blind studies in patients with a baseline IOP >24 mm Hg receiving latanoprost (n=271) or dorzolamide/timolol (n=273) also confirmed equivalent efficacy across a range of parameters. These included a 40% IOP reduction in 13% latanoprost recipients and 15% dorzolamide/timolol recipients, similar mean IOP reductions with high IOP at baseline (12.6 versus 12.5 mm Hg, respectively) and mean IOP at each time point during the day. Although these studies only included three month data, other studies have shown that the levels of IOP control with latanoprost and dorzolamide/timolol are maintained over 12 months.

Latanoprost versus pilocarpine/timolol fixed combination

A crossover study in 32 patients with primary open angle glaucoma or ocular hypertension compared latanoprost given once daily in the evening with pilocarpine/timolol maleate given twice daily for eight week treatment periods. Mean diurnal IOP (measured four times daily) was 24.1 + 2.4 mm Hg at baseline, and 16.8 + 2.1 mm Hg with pilocarpine/timolol after eight weeks, and 16.9 + 2.5 mm Hg with latanoprost after the same time period (p=0.60, nonsignificant difference). Only the 10.00 timepoint measurement was significantly lower with the pilocarpine/timolol fixed combination (15.9 + 2.3 versus 16.8 + 2.7 mm Hg; p=0.02). Although there were no significant differences in unsolicited systemic or ocular adverse events between the two treatments, the pilocarpine/timolol group showed a narrower pupil diameter, and a solicited adverse events survey revealed significantly more (p<0.001) blurred vision, stinging and ocular pain with this treatment.

Latanoprost versus brimonidine

Brimonidine is a highly selective α2-adrenergic agonist that increases uveoscleral outflow and reduces aqueous humour production in the eye. Several early studies suggested that greater or comparable IOP-lowering efficacy or fewer adverse events could be obtained with brimonidine compared with latanoprost, and this uncertainty prompted a systematic review by means of meta analysis of 14 comparative trials of the two antiglaucoma agents. This in fact showed that latanoprost was more effective than brimonidine as monotherapies in reducing IOP (weighted mean difference, WMD, 1.10 mm Hg; 95% CI 0.57-1.63), although significant heterogeneity was present in the data and the results showed greater WMD for studies where data were analysed for periods of more than six months and from studies of crossover design. The analysis also showed that fatigue was more commonly reported with brimonidine in these studies, although the incidence of other adverse events was similar between the two treatments. Three trials reported on ocular haemodynamics: latanoprost considerably increased ocular blood flow and peak systolic velocity in the ophthalmic artery, and ocular perfusion pressure, whereas brimonidine did not affect these parameters.

Latanoprost versus bimatoprost

Bimatoprost is a newer prostaglandin analogue to latanoprost, introduced in 2001 in the US. Early randomised studies showed that bimatoprost 0.03% was associated with lower IOP than latanoprost in patients with glaucoma and ocular hypertension, while other studies showed the two drugs had similar efficacy. A recent meta analysis of 13 randomised controlled trials comparing latanoprost and bimatoprost included 1302 patients treated for periods of between one and six months and concluded that bimatoprost resulted in greater reductions in morning IOP compared with latanoprost at all time points, with a weighted mean difference of 2.4-5.6% in percentage IOP reduction in favour of bimatoprost. Comparable proportions of patients reached IOP target levels on both drugs. Bimatoprost was associated with a significantly greater frequency of hyperaemia than latanoprost (rate difference of 20%; 95% CI 15-24%) although rates of serious ocular adverse events did not differ significantly between treatments.

Comparison with other prostaglandin analogues

Non-blind and double-blind trials of latanoprost versus unoprostone 0.15% for 1-2 months showed that mean IOP reduction with latanoprost is approximately double that associated with unoprostone, with six to eight times as many latanoprost recipients achieving an IOP reduction >30%. The IOP-lowering efficacy of latanoprost is generally similar to travoprost administered as a single daily dose of 0.0015% or 0.004% solution over 12 months.

Non-response to latanoprost

One published study has specifically examined the issue of non-response to latanoprost and whether such patients respond subsequently to other classes of antiglaucoma therapy. Rossetti at al treated 340 patients with primary open angle glaucoma or ocular hypertension with latanoprost for one month. Following this they were divided into three groups depending on the basis of IOP response: non-responders (defined as a <15% reduction), responders (>15-<30% reduction) and high responders (>30% reduction). The non-responders then entered a randomised crossover study evaluating the efficacy of timolol, brimonidine and pilocarpine. After one month's latanoprost treatment, mean IOP had reduced by about 30% (from 24.1 + 1.4 mm Hg at baseline to 16.9 + 2.4 mm Hg). There were 14 nonresponders (4.1%) and high responders accounted for 41.2%. The non-responders showed a significant further reduction with brimonidine treatment ($p<0.05$) with smaller, non-significant reductions with pilocarpine and timolol, although as the sample sizes were small, this must be taken into account. There are several drawbacks to this study. Firstly, it was a non-randomised prospective study with no control group. Secondly, the choice of a <15%

reduction in IOP to denote nonresponse was entirely arbitrary. Thirdly, the short duration of treatment with latanoprost was a limiting factor in that the true rate of non-response may have further reduced with a longer treatment period. However, the study does show that, according to the definition chosen here, the rate of non-response with latanoprost is low. Univariate and multivariate analyses showed no association between degree of response to latanoprost and baseline IOP, iris colour, eye axial length, refraction or anterior chamber angle width. Some degree of non-response is seen with all topical antiglaucoma therapies, and the fact that non-responders to latanoprost went on to demonstrate further reductions in IOP with alternative classes of topical antiglaucoma therapies may be due, for example, to differences in distribution of specific drug receptors between subjects, or to other genetic factors, since compliance as an obvious cause was ruled out by careful checking of patients by study personnel.

Long-term therapy with latanoprost in patients switched from other glaucoma therapies

Glaucoma medications are typically given for extended periods to maintain lowered IOP, and therefore efficacy and safety data are needed to ensure that there is no tachyphylaxis with long-term treatment and that local and systemic tolerability remain within acceptable limits and do not differ from the profile determined from short-term trials. A two year follow-up of 1571 patients treated with latanoprost 0.005% monotherapy in ophthalmology practices in Germany following switching from a range of other glaucoma medications was conducted by Bayer et al. The reasons for switching medication included inadequate IOP control or adverse events on existing therapy, poor compliance, or greater ease of dosing with latanoprost. Patients received a suite of baseline eye assessments including anterior segment examination (including slit-lamp examination), and applanation tonometry, visual assessment of iris colour and Snellen visual acuity. Visual field analyses and dilated fundoscopy were also performed. They were seen six-monthly and followed as long as possible. A total of 1376 patients completed 24 months latanoprost treatment. IOP decreased from a mean of 21.3 + 4.1 mm Hg at baseline to 17.6 + 3.2 mm Hg after switching to latanoprost from either mono- or adjunctive therapy ($p<0.001$). The IOP decreased across all diagnostic groups ($p<0.0001$), including primary open-angle, chronic angle-closure or exfoliation glaucoma, or ocular hypertension. The most common ocular adverse event was ocular irritation, reported in 25 patients (1.6%). Thus this study showed that latanoprost is capable of further reducing and maintaining a lowered IOP in patients switched from other antiglaucoma therapies for a period of at least two years.

Similar reductions in IOP (mean 20.1 + 3.9 at baseline to 17.1 + 3.5 mm Hg post-latanoprost; $p<0.0001$) were observed in another six month study in 3179 patients switched from a variety of other therapies. Over the duration of the study, virtually 90% of patients were maintained on latanoprost 0.005%. Another two year trial of latanoprost 0.005% monotherapy in 532 patients in UK and Scandinavia, of whom 493 completed six months, and 113 completed 24 months of treatment, showed that the greatest reduction in IOP occurred within the first two weeks (mean 8.2 mm (32%) Hg reduction). Thereafter, reductions were only modest, such that total mean IOP reduction was 8.9 mm Hg (34%) at 24 months, but demonstrated again that the initial mean IOP reduction was sustained throughout the trial period. Patients with an untreated IOP in the intervals 16-25, 26-29 and 30-45 mm Hg showed a 97%, 90% and 78% chance, respectively, of achieving a sufficient IOP reduction (deemed as >15% change from baseline) with latanoprost during two years of treatment. Patients with primary open angle glaucoma showed an 86% chance of achieving a sufficient IOP reduction; the figure for those with ocular hypertension was 97% ($p<0.01$). An increase, or a high risk for an increase, in iris pigmentation, was the main reason for adverse event withdrawal in the study.

Latanoprost has been in clinical use since 1996 and has well-established efficacy in the treatment of open angle glaucoma and ocular hypertension.
Data from several clinical trials (as detailed in the literature review provided by the applicant) have shown that latanoprost given as monotherapy or in combination with other IOP lowering agents at the recommended dose (one drop of latanoprost 0.005% instilled every evening) effectively decreases intraocular pressure in patients with open-angle glaucoma or ocular hypertension and that the treatment is well tolerated. Evening administration of latanoprost has been shown to be more efficacious than morning instillation. It has been shown that once daily dosing with latanoprost maintains its IOP lowering effect over a 24 hour period.
With regards the therapeutic equivalence data derived from study APT01, 95% confidence interval of the difference in change of mean diurnal IOP from day 1 to day 29 between the Test Product and the Reference Product was well within the pre-defined limits of ±1.5 mmHg.

Clinical safety
Introduction

The safety aspect of study APT01 has been dealt with under section III.1.1. of this document (main study). No new applicant generated data submitted otherwise. This section is based on a literature review provided by the applicant.
Overall, latanoprost ophthalmic solution is a well-tolerated treatment in glaucoma and ocular hypertension, with adverse events being mild and reversible upon treatment discontinuation.

Adverse events
Local effects resulting from ocular instillation of latanoprost include blurred vision, burning, stinging, conjunctival hyperaemia, foreign body sensation, increased pigmentation, eyelid oedema and punctate epithelial keratopathy. They have been reported in between 5 and 15% of patients in controlled trials.
Conjunctival hyperaemia occurs within the first two days of latanoprost, and other topical prostaglandin treatments, diminishes with time and is mild in the majority of patients. Its incidence has been about 14% in two trials, similar or lower than that reported with bimatoprost, but higher than with brimonidine in another six week trial (36% versus 9%), although incidences become similar (6%) after six months.
There have been rare reports of iritis and/or uveitis and macular oedema in association with topical latanoprost. Macular oedema has mainly occurred in aphakic patients, in pseudoaphakic patients with torn posterior lens capsules or anterior chamber lenses, or in patients with risk factors for cystoid macular oedema such as diabetic retinopathy or retinal vein occlusion. Two cases of herpes simplex dendritic keratitis have been reported in patients during latanoprost therapy.
Darkening, thickening or lengthening of the eyelashes has also occurred in some of the latanoprost recipients in published clinical studies. These effects are reversible upon stopping treatment.
In terms of special studies examining other aspects of ocular safety with topical latanoprost 0.005%, it is known that single daily doses of the drug given for four weeks do not adversely affect tear fluid or ocular surface condition of the eyes of patients with bilateral primary open angle glaucoma, as any effects on tear break-up time or Rose-Bengal staining of the corneas remain within the normal ranges.
Systemic adverse events are infrequent with latanoprost because the drug and its metabolites have relatively short elimination half-lives. In contrast to timolol, latanoprost is associated with minimal systemic adverse effects. Although transient elevated blood pressure of 200/120 mm Hg and 260/120 mm Hg has been reported in two cases in elderly subjects with

no prior history of hypertension within four days and six weeks, respectively, of starting latanoprost, a range of other studies have reported that opthalmic use of latanoprost is not associated with significant changes in blood pressure or heart rate. Chest pain and/or angina pectoris were reported in 1-2% of patients treated with latanoprost.
During clinical trials with latanoprost, the most common systemic adverse event was respiratory tract infection, colds or flu (incidence approximately 4%) although the incidence of these symptoms in control groups is not stated. Ocular administration of latanoprost in patients with asthma does not cause bronchoconstriction, although there are occasional reports of asthma and dyspnoea with therapeutic use in postmarketing experience. Facial rash has been reported in an elderly female after five days of latanoprost use which resolved on drug withdrawal and may have been a hypersensitivity response. Muscle, joint and back pain have occurred in 1-2% of latanoprost recipients.

Long-term tolerability and safety of latanoprost
The commonest ocular adverse event seen with latanoprost in one six month study in patients switched from other antiglaucoma therapies was conjunctival hyperaemia (2%) and the commonest systemic adverse event was headache (0.2%). In another two year follow-up of 1571 patients on latanoprost monotherapy 0.005%, the most frequently reported local adverse event was ocular irritation (1.6%). A 12 month double-blind study examined corneal endothelial cell density and corneal thickness in patients with bilateral ocular hypertension or open angle glaucoma (and with clinically normal corneas at baseline) subsequently treated with once daily latanoprost or timolol as monotherapies, or in combination. At the end of the study there were no significant changes from baseline in corneal endothelial cell density and corneal thickness in any of the treatment groups, confirming that latanoprost is not associated with any adverse corneal changes when given long-term.
Latanoprost may gradually (over months to years of use) result in increased brown pigmentation in the iris by increasing the number of melanosomes in melanocytes. The onset of pigmentation is usually within the first eight months of treatment and more rarely during a second or third year. The usual pattern of iris pigmentation from latanoprost spreads concentrically towards the periphery, although the entire iris may be affected in some individuals. Although no further change in iris colour occurs after withdrawing latanoprost treatment, colour changes induced by the drug may be permanent and heterochromia has resulted from patients treating one eye. It has been reported to occur in 5% of 247 patients treated with latanoprost as a definite or possible harmless effect in one study and in 18% of 277 patients treated for 24 months in a second study. It is also known that 16-20% of patients treated with the originator product Xalatan® for up to one year (33% after five years) show this phenomenon. The phenomenon is predominantly observed in patients with mixed colour irides. It is also associated with age, since significantly more patients aged >75 years developed iris pigmentation following latanoprost 0.005% therapy for six months than those aged <60 years (77.8% versus 22.2%; p=0.0001) in one study. A recent open five year safety surveillance study of latanoprost versus usual care (any other commercially available topical antiglaucoma medication) examined ocular adverse events in 5854 patients (3936 receiving latanoprost, 1918 receiving usual care) in 14 countries. This study sample gave an 80% power with a 2:1 allocation latanoprost: usual care to detect an additional incidence of 1% in an adverse event to latanoprost if the true incidence of the adverse event was 1%, with a significance level of p=0.05. Patients were examined at baseline and every six months for five years. A total of 2707 (69%) patients initially randomised to latanoprost completed the study and 4638 (79.2%) received at least one dose of latanoprost. The incidence of new ocular adverse events (corneal erosions, iritis / uveitis or macular oedema) over the 5-year period was <3.2% for both groups, serious adverse events occurred in a similar incidence of patients: 0.43% in the latanoprost group, 0.47% in the usual care group. Those resulting in

treatment discontinuation in the latanoprost group included cystoid macular oedema (n=4), uveitis (n=3), chest pain, eye irritation, headache, dermatitis due to eyedrop allergy, conjunctivitis, dyspnoea and macula lutea degeneration (n=1 each). Only 12.4% of patients treated with latanoprost developed iris pigmentation, 40.3% experienced eyelash changes and 7.8% had increased pigmentation of the periorobital skin. No serious adverse events were seen in the patients who developed increased iris pigmentation. One drawback to this study is that patients were treated according to routine medical practice and investigators were free to modify the therapy of any patient in either group. Because a large proportion of patients in this study received both latanoprost and usual care over the five year study period, no meaningful statistical comparisons could be made between treatments. However, despite this drawback, the study showed that serious ocular adverse events are low in incidence with latanoprost and that the drug is not associated with any increased safety risk long-term compared with other antiglaucoma therapies.

Post marketing experience/Risk management

This generic medicinal product has not been marketed before.
Latanoprost 0.005% eye drop has been available on the market for more than 10 years and its safety is well-established. Therefore a Risk Management Plan is not mandatory, in line with ***Section 3 of VOLUME 9A of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use (September 2008)***.

Proposals for post authorisation follow up (post marketing surveillance)

The applicant proposes to use the European Harmonised Birth Date (EU HBD) and associated Data Lock Point (DLP) as published by the Heads of Medicines Agencies. For Latanoprost the EU HBD is 05 June 1996 and the first agreed DLP after submission is 28 February 2012. This implies that the applicant proposes to submit the first PSUR taking 28 February 2012 as DLP, with subsequent PSURs every 3 years based on this DLP.

The applicant's proposal is in line with ***Article 104 of directive 2001/83/EC (as amended)*** and therefore acceptable.

The safety aspect of study APT01 has been dealt under section III.1.1. of this document (main study). The applicant has not generated new clinical data otherwise.

The most common ADRs with latanoprost 0.005% eye drop are increased iris pigmentation, mild to moderate conjunctival hyperaemia, eye irritation, eyelash and vellus hair changes (increased length, thickness, pigmentation and number) vast majority of reports in the Japanese population.
Latanoprost 0.005% eye drop has been on the market for more than 10 years and has a well-known safety profile. Pending adequate demonstration of therapeutic equivalence of the test and the reference products, the overall benefit risk balance can be considered positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPC, PIL and labelling are medically satisfactory and consistent with those for the reference product.

Clinical Expert Report

The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Marketing Authorisation Application (MAA) Forms

The MAA form is satisfactory.

Clinical Conclusion

There are no objections to the approval of this product from a clinical point of view.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Latanoprost 0.005% w/v Eye Drops, Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRE-CLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

This application is for generic medicinal product of Xalatan 0.005% Eye drops, (PL 00032/0220), which was originally granted to Pharmacia Limited, UK, on the 16th December 1996. The use of the reference product is well-established in the UK.

No new safety data are supplied or required for this generic application. Latanoprost has a well-established side-effect profile and is generally well-tolerated.

The SmPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's product and the innovator product are essentially similar. Extensive clinical experience with latanoprost is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome