BRIDGING REPORT

Bridging Study of the Package Information Leaflet for:

[Invented name] 40 micrograms/mL+ 5 mg/mL eye drops, solution
travoprost/timolol

Date: 02/08/2016

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1. Introduction

According to the directive Article 59(3) of Directive 2001/83/EC as amended by directive 2004/27/EC, **ELC Group** confirms that the Package Information Leaflet for **[Invented name] 40 micrograms/mL+ 5 mg/mL eye drops, solution, Preservative free** (henceforth referred to as the Daughter PIL) contains the required statutory information. Furthermore, it is confirmed that the Daughter Package Information Leaflet is similar to the Package Information Leaflet for **[Invented name] 40 micrograms/mL+ 5 mg/mL eye drops, solution** (henceforth referred to as the Parent PIL), and therefore requires no separate user testing.

The basis for this report and its evaluation comes from both the European Commission (Article 59(3) of Council Directive 2001/83/EC and also by Article 63(2) of Directive 2001/83/EC as amended), the European Commission document "Guideline on the readability of the labelling and package leaflet of medicinal products for human use" (2009), Recommendations for Bridging from CMDh (April 2009, revision 1) and MHRA guidance on bridging (Guidance for the Pharmaceutical Industry on the use of BRIDGING STUDIES to demonstrate compliance with article 59(3) of Council Directive 2001/83/EC [Consultation with Target Patient Groups]), as well as specific information and feedback obtained by ELC Group from the relevant authorities on the use of bridging in user testing schemes.

Differences between the Daughter PIL and the Parent PIL are presented with analysis and evidence which show that these differences have little material impact on readability. Results from the readability testing study of the Parent PIL should therefore be extrapolated to the Daughter PIL**.** For complete analysis and results of the full user test performed on the Parent PIL please refer to the final outcome report: *Readability Test of the Package Information Leaflet for: **[Invented name] 40 micrograms/mL+ 5 mg/mL eye drops, solution** (April 25, 2016).*

Name of the Daughter PIL:

[Invented name] 40 micrograms/mL+ 5 mg/mL eye drops, solution, Preservative Free
travoprost/timolol

Name of the Parent PIL:

[Invented name] 40 micrograms/mL+ 5 mg/mL eye drops, solution
travoprost/timolol

Marketing Authorisation Holder/Applicant:

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This report was prepared by:

Name:
Title: Life Sciences Project Manager

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2. Product Descriptions

Daughter PIL

Travoprost/Timolol eye drops solution is a combination of two active substances (travoprost and timolol). Travoprost is a prostaglandin analogue which works by increasing the outflow of liquid of the eye, which lowers its pressure. Timolol is a beta blocker which works by reducing the production of fluid within the eye. The two substances work together to reduce pressure within the eye.

Travoprost/Timolol eye drops are used to treat high pressure in the eye in adults, including the elderly**.** This pressure can lead to an illness called glaucoma.
Travoprost/Timolol eye drops solution is a sterile solution that does not contain a preservative.

Parent PIL

Travoprost/Timolol eye drops solution is a combination of two active substances (travoprost and timolol). Travoprost is a prostaglandin analogue which works by increasing the outflow of liquid of the eye, which lowers its pressure. Timolol is a beta blocker which works by reducing the production of fluid within the eye. The two substances work together to reduce pressure within the eye.

Travoprost/Timolol eye drops are used to treat high pressure in the eye in adults, including the elderly**.** This pressure can lead to an illness called glaucoma.

3. Summary of the Bridging Process

Any differences between the two PILs in both the textual and visual presentations are outlined and analysed in this report. Once any and all differences have been acknowledged, addressed and discussed, it will be shown that the Daughter PIL requires no separate user testing due to its similarity to the already tested Parent PIL.

3.1 Aspects Investigated and Methodology Used

The Daughter PIL proposed for bridging and the Parent PIL were compared based on the following criteria:

- **Visual Presentation**: leaflet dimension, font, font size, coloring scheme, spacing, format, organization of sections and any graphics used in the PIL.
- **Contents**: key safety messages including indications, contraindications, side effects, ingredients, storage information, and any other relevant data.

3.2 Detailed Bridging Procedure

1. Readability testing was conducted on the Parent PIL**.**
2. Initial review and comparison of the Daughter and the Parent PIL based on the criteria above.
3. It was concluded that the Daughter PIL is similar to the Parent PIL.
4. A mock up was created for the Daughter PIL that is as similar as possible to the Parent PIL.
5. Differences between the Daughter PIL and the Parent PIL were analysed.
6. This final bridging report was created.

4. Timeline

5. Bridging Analysis Results

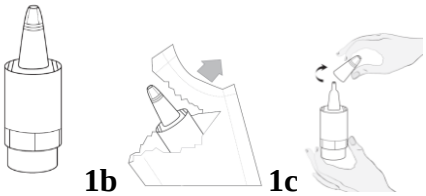
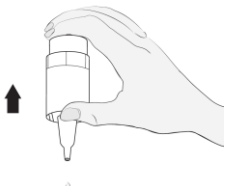
According to the guidance on the use of bridging studies, bridging is acceptable for Package Leaflets with minor differences. The content analysis to follow will look at the key differences and corresponding justifications so that each difference is deemed to be acceptable and/or of minimal significance.

5.1 Differences in Leaflet Content

This portion of the bridging study focuses on content present in the Daughter PIL and not present in the Parent PIL, since the contents of the Parent PIL have successfully completed readability testing. The following table highlights and discusses these differences.

Table 1. Differences by Package Leaflet Section

	Parent PIL	Daughter PIL
Section #1	[Not listed]	[Invented name] eye drops solution is a sterile solution that does not contain a preservative.
Discussion	The Daughtre PIL contains additional information which does not apply to the medicine in the Parent PIL. The supplimentary sentence is for information purpose only and doesn't contain any intructions for use. Moreover, it is written using uncomplicated wording. Consequently, this difference will not affect the readability and no testing is needed for this part of the Daughter PIL.	
Section #2	**[Invented name] contains benzalkonium chloride** This medicine contains benzalkonium chloride, which may cause eye irritation. Avoid contact with soft contact lenses. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Known to discolour soft contact lenses.	[Not listed]
	[Invented name] contains macrogolglycerol hydroxystearate 40 This medicine contains macrogolglycerol hydroxystearate 40, which may cause skin reactions.	**[Invented name] contains macrogolglycerol hydroxystearate 40 and propylene glycol** which may cause skin reactions and irritation.

	Parent PIL	Daughter PIL
Discussion	The Parent PIL provides information on the excipients (preservative) which is not listed in the Daughter PIL, as the medicine in the Daughter PIL is preservative free. Since the Parent PIL can be deemed more complex in this instance and it successfully passed readability testing criteria, the additional testing should not be required for the Daughter PIL on account of this differences.	
Section #3	**Instructions for use**  • Immediately before using a bottle for the first time, tear-off the sachet **(picture 1).** Take out the bottle and write the date of opening on the label in the space provided. • […] • Twist off the cap.	**Instructions for use**  **1a** **1b** **1c** • Take the multi-dose container **(picture 1a)** out of the carton box. If the container is stored within an overwrap pouch, tear – off to open **(picture 1b)** and write the date of opening on the carton box and the bottle in the space provided. • […] • Remove the cap **(picture 1c)**.
Discussion	The instructions in both PILs are similar, however there are some wording differences (see underlined) due to the different packaging. The wording used in the Daughter PIL is clear and user-friendly, therefore the readability should not be affected. Additionally, this information in the Daughter PIL has been subjected to a full and complete Readability Focus Test. For detailed analysis and presentation of the results please refer to the outcome report '*Readability Focus Test of the Package Information Leaflet for: [Invented name] 40 micrograms/mL+ 5 mg/mL eye drops, solution', from July 29, 2016.*	
Section #3	[Not listed] • Hold the bottle, pointing down, between your thumb and fingers.	 **2** • Hold the bottle upside down with the thumb on the shoulder

	Parent PIL	Daughter PIL
		of the bottle and the other fingers on the bottom of the bottle. Before the first use, pump the bottle repeatedly, approximately 10 times, until the first drop emerges **(picture 2)**.
	 […]	**3**  […]
Discussion	The Daughter PIL contains the additional diagram and slightly different instructions on how to handle the medicine bottle. This information in the Daughter PIL has been subjected to a full and complete Readability Focus Test. For detailed analysis and presentation of the results please refer to the outcome report '*Readability Focus Test of the Package Information Leaflet for: [Invented name] 40 micrograms/mL+ 5 mg/mL eye drops, solution', from July 29, 2016.*	
Section #3	 • **[…]** Gently squeeze the bottle to release one drop of medicine at a time **(picture 3)**. [Listed below]  • […] • Close the bottle cap firmly immediately after use. • Only use one bottle of medicine at a	**4**  • […] • Gently press down on the bottom side of the bottle to release one drop of medicine at a time **(picture 4)**. • If a drop misses your eye, try again. **5**  • […] • Close the multi-dose container cap firmly immediately after use. • Only use one bottle of medicine

	Parent PIL	Daughter PIL
	time. Do not open the sachet until you need to use the bottle. **You must throw away the bottle 4 weeks after you first opened it**, to prevent infections, and use a new bottle.	at a time. Do not open the cap until you need to use the multi-dose container. **You must throw away the bottle 28 days after you first opened it,** to prevent infections, and use a new bottle.
	If a drop misses your eye, try again.	[Listed above]
Discussion	The instructions and the diagrams are slightly different in both PILs (see underlined). The information in the Daughter PIL has been subjected to a full and complete Readability Focus Test. For detailed analysis and presentation of the results please refer to the outcome report '*Readability Focus Test of the Package Information Leaflet for: [Invented name] 40 micrograms/mL+ 5 mg/mL eye drops, solution', from July 29, 2016.*	
Section #5	[…]	[…]
	[Not listed]	Do not use this medicine if you notice that the multi dose container has been broken or damaged before you first open it.
	Before opening, keep the bottle in the sachet in order to protect from moisture. After first opening, this medicine does not require any special storage conditions.	This medicinal product does not require any special temperature storage conditions.
	You must throw away the bottle 4 weeks after you first opened it, to prevent infections, and use a new bottle. […]	**You must throw away the bottle 28 days after you first opened it,** to prevent infections, and use a new bottle. […]
Discussion	The Daughter PIL lists additional information on the storage of the medicine, which is not mentioned in the Parent PIL. The wording used in the Daughter PIL is uncomplicated and will not affect the overall readability. Additionally, this information in the Daughter PIL has been subjected to a full and complete Readability Focus Test. For detailed analysis and presentation of the results please refer to the outcome report '*Readability Focus Test of the Package Information Leaflet for: [Invented name] 40 micrograms/mL+ 5 mg/mL eye drops, solution', from July 29, 2016.*	

	Parent PIL	Daughter PIL
Section #6	**What [Invented name] contains** […] • The other ingredients are benzalkonium chloride solution 50% w/v, macrogolglycerol hydroxystearate (nominal value:40), trometamol, edetate disodium, boric acid, mannitol, sodium hydroxide 5N and water for injection. **What [Invented name] looks like and contents of the pack** [Invented name] eye drops, solution is presented as a clear, colorless, aqueous solution supplied in packs containing [X] polypropylene vials of 5ml with white opaque LDPE nozzle and a white opaque HDPE/LDPE cap with tamper proof seal. Each bottle is enclosed in a sachet. Each bottle contains 2.5 ml solution.	**What [Invented name] contains** […] • The other ingredients are mannitol, boric acid, sodium hydroxide, macrogolglycerol hydroxystearate (nominal value: 40), propylene glycol, sodium chloride and water purified. **What [Invented name] looks like and contents of the pack** [Invented name] eye drops, solution is presented as a 2.5 ml clear, colorless, aqueous solution in a cardboard box containing a 5 ml white plastic multi-dose container. The multi – dose container can be available in an overwrap, inside the cardboard box. The product is available in the following pack sizes: Cartons containing [X] number of bottles.
Discussion	All information is presented using the same style and format. Since the Parent PIL has successfully completed user testing and the Daughter PIL is no more complicated than the Parent PIL in this instance, no separate user testing should be required.	

5.2 Layout, Style and Language

Layout and style

	Parent PIL	Daughter PIL
Body Text		
Headings		
PIL Dimension		
Colouring Scheme		
Columns	Two columns	Two columns
Format	Double-sided	Double-sided
Discussion	The Daughter PIL and the Parent PIL are very similar in both style and layout. The use of an index, numbered section headings and bold sub-headings were implemented consistently throughout both leaflets. Additionally, text is left-aligned and techniques to improve readability such as bullet-point lists, line spacing and bold font were applied in similar ways throughout both PILs. Howevere, the size of the leaflets are not the same. The overall dimension of the Daughter PIL is smaller, which makes it easier to handle the leaflet. Since both PILs follow the same two-column format that allows users to navigate through the text the same manner, the readability of the Daughter PIL will not be affected, and therefore no separate testing should be needed on account of this difference.	

Language

Both PILs were written in English according to the QRD template. Except where indicated in

Section 5.1, as well as where the Parent PIL serves as a more complex PIL, identical sentences were used for the information presented in both PILs.

6. Conclusion

In conclusion, this analysis is able to clearly establish that the leaflet text and mockup format for **[Invented name] 40 micrograms/mL+ 5 mg/mL eye drops, solution, Preservative Free** (Daughter PIL) is strongly similar to **[Invented name] 40 micrograms/mL+ 5 mg/mL eye drops, solution** (Parent PIL). The results of this bridging study indicate that the leaflet for Daughter PIL is well structured and organized, easy to understand and written in a comprehensible manner and therefore requires no separate user testing.

ELC also confirms the report conforms to the principles and success criteria featured in the European Commission's document “Consultation With Target Patient Groups - Meeting The Requirements Of Article 59(3) Without The Need For A Full Test - Recommendations For Bridging” (Revision 1, April 2009).

Based on the above mentioned facts the package leaflet can be qualified as ACCEPTABLE.

Life Sciences Project Manager

7. Appendices

Appendix 1 - The Package Leaflet for the Daughter PIL: **[Invented name] 40 micrograms/mL+ 5 mg/mL eye drops, solution, Preservative Free**

Package leaflet: Information for the user

[Invented name] 40 micrograms/mL+ 5 mg/ mL eye drops, solution
travoprost/timolol

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What [Invented name] is and what it is used for

[Invented name] eye drops solution is a combination of two active substances (travoprost and timolol). Travoprost is a prostaglandin analogue which works by increasing the outflow of liquid of the eye, which lowers its pressure. Timolol is a beta blocker which works by reducing the production of fluid within the eye. The two substances work together to reduce pressure within the eye.

[Invented name] eye drops are used to treat high pressure in the eye in adults, including the elderly. This pressure can lead to an illness called glaucoma.
[Invented name] eye drops solution is a sterile solution that does not contain a preservative.

2. What you need to know before you use [Invented name]

Do not use [Invented name]:
- if you are allergic to travoprost, timolol, or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to any prostaglandins or beta-blockers
- if you have now or have had in the past respiratory problems such as asthma, severe chronic obstructive bronchitis (severe lung disease which may cause wheeziness, difficulty in breathing and/or long standing cough, or other types of breathing problems
- if you have severe hay fever
- if you have a slow heart beat, heart failure or disorders of heart rhythm (irregular heart beats)
- if the surface of your eye is cloudy

Ask your doctor for advice if any of these apply to you.

Warnings and precautions
Talk to your doctor or pharmacist before using [Invented name] if you have now or have had in the past:

- coronary heart disease (symptoms can include chest pain or tightness, breathlessness or choking), heart failure, low blood pressure
- disturbances of heart rate such as slow heart beat
- breathing problems, asthma or chronic obstructive pulmonary disease
- poor blood circulation disease (such as Raynaud's disease or Raynaud's syndrome)
- diabetes, as timolol may mask signs and symptoms of low blood sugar
- overactivity of the thyroid gland as timolol may mask signs and symptoms of thyroid disease
- myasthenia gravis (chronic neuromuscular weakness)
- any severe allergic reaction (skin rash, redness and itching of the eye) while using [Invented name], whatever the cause, adrenaline treatment may not be as effective. So when receiving any other treatment please tell the doctor that you are using [Invented name]
- a cataract surgery
- an eye inflammation

Tell your doctor before you have an operation that you are using [Invented name] as timolol may change effects of some medicines used during **anaesthesia**.

[Invented name] may change the colour of your iris (the coloured part of your eye). This change may be permanent.
[Invented name] may increase the length, thickness, colour and/or number of your eyelashes and may cause unusual hair growth on your eyelids.

Travoprost may be absorbed through the skin and therefore should not be used by women who are pregnant or are attempting to become pregnant. If any of the medicine comes into contact with the skin then it should be washed off straight away.

Children
[Invented name] is not to be used by children and adolescents under 18 years of age.

Other medicines and [Invented name]
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
[Invented name] can affect or be affected by other medicines you are using, including other eye drops for the treatment of glaucoma. Tell your doctor if you are using or intend to use
- medicines to lower blood pressure,
- heart medicine including quinidine (used to treat heart conditions and some types of malaria),
- medicines to treat diabetes or antidepressants known as fluoxetine and paroxetine.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Do not use [Invented name] if you are pregnant unless your doctor considers it necessary. If you could get pregnant you must use adequate contraception whilst you use the medicine.

Do not use [Invented name] if you are breast-feeding. This medicine may get into your milk.

Driving and using machines
You may find that your vision is blurred for a time just after you use [Invented name]. Do not drive or use machines until this has worn off.

[Invented name] contains macrogolglycerol hydroxystearate 40 and propylene glycol
which may cause skin reactions and irritation.

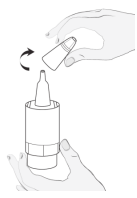
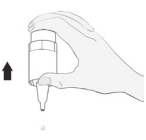
3. How to use [Invented name]

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is
One drop in the affected eye or eyes, once a day-in the morning or in the evening. Use at the same time each day.
Only use [Invented name] in both eyes if your doctor told you to do so. Use it for as long as your doctor told you to.

Only use [Invented name] for dropping in your eyes.

Instructions for use

 **1a**  **1b**  **1c**	• Take the multi-dose container **(picture 1a)** out of the carton box. If the container is stored within an overwrap pouch, tear – off to open **(picture 1b)** and write the date of opening on the carton box and the bottle in the space provided. • Get the medicine bottle and a mirror. • Wash your hands. • Remove the cap **(picture 1c)**.
 **2**	• Hold the bottle upside down with the thumb on the shoulder of the bottle and the other fingers on the bottom of the bottle. Before the first use, pump the bottle repeatedly, approximately 10 times, until the first drop emerges **(picture 2)**.
 **3**	• Tilt your head back. Pull down your eyelid with a clean finger, until there is a 'pocket' between the eyelid and your eye. The drop will go in here **(picture 3)**. • Bring the bottle tip close to the eye. Use the mirror if it helps.
 **4**  **5**	• **Do not touch your eye or eyelid, surrounding areas or other surfaces with the dropper.** It could infect the drops. • Gently press down on the bottom side of the bottle to release one drop of medicine at a time **(picture 4)**. • If a drop misses your eye, try again. • After using the medicine, press a finger into the corner of your eye, by the nose **(picture 5)**. This helps to stop the medicine getting into the rest of the body.

	• If you use drops in both eyes, repeat these same steps for your other eye. • Close the multi-dose container cap firmly immediately after use. • Only use one bottle of medicine at a time. Do not open the cap until you need to use the multi-dose container. • **You must throw away the bottle 28 days after you first opened it,** to prevent infections, and use a new bottle.

If you use more [Invented name] than you should
If you use more [Invented name] than you should, rinse it all out with warm water. Do not put in any more drops until it is time for your next regular dose.

If you forget to use [Invented name]
If you forget to use [Invented name], continue with the next dose as planned. Do not use a double dose to make up for a forgotten dose. The dose should not exceed one daily drop in the affected eye(s).

If you stop using [Invented name]
If you stop using [Invented name] without speaking to your doctor the pressure in your eye will not be controlled which could lead to loss of sight.

If you are using other eye drops, leave at least 5 minutes between putting in [Invented name] and the other drops.

If you wear soft contact lenses do not use the drops with your lenses in. After using the drops wait 15 minutes before putting your lenses back in.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

You can usually carry on taking the drops, unless the effects are serious. If you're worried, talk to a doctor or pharmacist. Do not stop using [Invented name] without speaking to your doctor.

Very common (may affect more than 1 in 10 people):
Effects in the eye: eye redness

Common (may affect up to 1 in 10 people):
Effects in the eye: eye surface inflammation with surface damage, eye pain, blurred vision, abnormal vision, dry eye, itchy eye, eye discomfort, signs and symptoms of eye irritation (e.g. burning, stinging).

Uncommon (may affect up to 1 in 100 people):
Effects in the eye: inflammation of the eye surface, inflammation of the eyelid, swollen conjunctiva, increased growth of eyelashes, iris inflammation, eye inflammation, sensitivity to light, reduced vision, tired eyes, eye allergy, eye swelling, increased tear production, eyelid redness, eyelid colour change
General side effects: drug allergy, dizziness, headache, increased or decreased blood pressure, shortness of breath, excessive hair growth, drip at back of throat, skin inflammation and itching, decreased heart rate.
Rare side effects (may affect up to 1 in 1,000 people):
Effects in the eye: thinning of the eye surface, inflammation of the eyelid glands, broken blood vessel in the eye, eyelid crusting, abnormally positioned eyelashes, abnormal growth of lashes.
General side effects: nervousness, irregular heart rate, loss of hair, voice disorders, difficulty breathing, cough, throat irritation, hives, abnormal liver blood tests, skin discolouration, skin darkening, thirst, tiredness, discomfort inside of nose, coloured urine, pain in hands and feet.

Not known (frequency cannot be estimated from the available data):
Effects in the eye: droopy eyelid (making the eye stay half closed)

General side effects: rash, heart failure, chest pain, stroke, fainting, depression, asthma, increased heart rate, numbness or tingling sensation, palpitations, swelling in the lower limbs, bad taste.

Additionally:
[Invented name] is a combination of 2 active substances. Like other medicines applied into eyes, travoprost and timolol (a beta-blocker) are absorbed into the blood. This may cause similar side effects as seen with intraveneous and/or oral beta-blocking medicines. The incidence of side effects after topical ophthalmic administration is lower than when medicines are, for example, taken by mouth or injected. Listed side effects which include reactions seen within the class of beta-blockers when used for treating eye conditions are as follows:

Effects in the eye: inflammation of the eyelid, inflammation in the cornea, detachment of the layer below the retina that contains blood vessels following filtration surgery which may cause visual disturbances, decreased corneal sensitivity, corneal erosion (damage to the front layer of the eyeball), double vision, changes in the colour of the iris

General side effects:
- Heart and circulation: slow heart rate, palpitations, oedema (fluid build up), changes in the rhythm or speed of the heartbeat, congestive heart failure (heart disease with shortness of breath and swelling of the feet and legs due to fluid build up), a type of heart rhythm disorder, heart attack low blood pressure, Raynaud's phenomenon, cold hands and feet, reduced blood supply to the brain.
- Respiratory: constriction of the airways in the lungs (predominantly in patients with pre-existing disease), difficulty breathing, stuffy nose
- Nervous system and general disorders: difficulty sleeping (insomnia), nightmares, memory loss loss of strength and energy
- Gastric: taste disturbances, nausea, indigestion, diarrhea, dry mouth, abdominal pain, vomiting
- Allergy: generalized allergic reactions including swelling beneath the skin that can occur in areas such as the face and limbs, and can obstruct the airway which may cause difficulty swallowing or breathing, localized and generalized rash, itchiness, severe sudden life-threatening allergic reaction.
- Skin: skin rash with white silvery coloured appearance (psoriasiform rash) or worsening of psoriasis, peeling skin
- Muscular: increases in signs and symptoms of myasthenia gravis (muscle disorder), unusual sensations like pins and needles, muscle weakness/tiredness, muscle pain not caused by exercise
- Reproduction: sexual dysfunction, decreased libido
- Metabolism: low blood sugar levels

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system <to be completed nationally>. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store [Invented name]

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle after EXP. The expiry date refers to the last day of that month.

Do not use this medicine if you notice that the multi dose container has been broken or damaged before you first open it.

This medicinal product does not require any special temperature storage conditions.

You must throw away the bottle 28 days after you first opened it, to prevent infections, and use a new bottle. Write down the date you opened the bottle in the space the bottle label and box.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What [Invented name] contains

- The active substances are travoprost and timolol.
- Each mL of solution contains 40 micrograms of travoprost and 5 mg of timolol (as timolol maleate).
- The other ingredients are mannitol, boric acid, sodium hydroxide, macrogolglycerol hydroxystearate (nominal value: 40), propylene glycol, sodium chloride and water purified.

What [Invented name] looks like and contents of the pack

[Invented name] eye drops, solution is presented as a 2.5 ml clear, colorless, aqueous solution in a cardboard box containing a 5 ml white plastic multi-dose container.

The multi – dose container can be available in an overwrap, inside the cardboard box.

The product is available in the following pack sizes:

Cartons containing [X] number of bottles.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

<[To be completed nationally]>

This leaflet was last revised in

Pharmathen

Appendix 2 - The Package Leaflet for the Parent PIL: **[Invented name] 40 micrograms/mL+ 5 mg/mL eye drops, solution**

Package leaflet: Information for the user

[Invented name] 40 micrograms/mL+ 5 mg/mL eye drops, solution
travoprost/timolol

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What [Invented name] is and what it is used for

[Invented name] eye drops solution is a combination of two active substances (travoprost and timolol). Travoprost is a prostaglandin analogue which works by increasing the outflow of liquid of the eye, which lowers its pressure. Timolol is a beta blocker which works by reducing the production of fluid within the eye. The two substances work together to reduce pressure within the eye.

[Invented name] eye drops are used to treat high pressure in the eye in adults, including the elderly**.** This pressure can lead to an illness called glaucoma.

2. What you need to know before you use [Invented name]

Do not use [Invented name]:
- if you are allergic to travoprost, timolol, or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to any prostaglandins or beta-blockers
- if you have now or have had in the past respiratory problems such as asthma, severe chronic obstructive bronchitis (severe lung disease which may cause wheeziness, difficulty in breathing and/or long standing cough, or other types of breathing problems
- if you have severe hay fever
- if you have a slow heart beat, heart failure or disorders of heart rhythm (irregular heart beats)
- if the surface of your eye is cloudy

Ask your doctor for advice if any of these apply to you.

Warnings and precautions
Talk to your doctor or pharmacist before using [Invented name] if you have now or have had in the past:

- coronary heart disease (symptoms can include chest pain or tightness, breathlessness or choking), heart failure, low blood pressure
- disturbances of heart rate such as slow heart beat
- breathing problems, asthma or chronic obstructive pulmonary disease
- poor blood circulation disease (such as Raynaud's disease or Raynaud's syndrome)
- diabetes, as timolol may mask signs and symptoms of low blood sugar
- overactivity of the thyroid gland as timolol may mask signs and symptoms of thyroid disease
- myasthenia gravis (chronic neuromuscular weakness)
- any severe allergic reaction (skin rash, redness and itching of the eye) while using [Invented name], whatever the cause, adrenaline treatment may not be as effective. So when receiving any other treatment please tell the doctor that you are using [Invented name]
- a cataract surgery
- an eye inflammation

Tell your doctor before you have an operation that you are using [Invented name] as timolol may change effects of some medicines used during **anaesthesia.**

[Invented name] may change the colour of your iris (the coloured part of your eye). This change may be permanent.
[Invented name] may increase the length, thickness, colour and/or number of your eyelashes and may cause unusual hair growth on your eyelids.

Travoprost may be absorbed through the skin and therefore should not be used by women who are pregnant or are attempting to become pregnant. If any of the medicin comes into contact with the skin then it should be washed off straight away.

Children
[Invented name] is not to be used by children and adolescents under 18 years of age.

Other medicines and [Invented name]
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
[Invented name] can affect or be affected by other medicines you are using, including other eye drops for the treatment of glaucoma. Tell your doctor if you are using or intend to use
- medicines to lower blood pressure,
- heart medicine including quinidine (used to treat heart conditions and some types of malaria),
- medicines to treat diabetes or antidepressants known as fluoxtine and paroxetine.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Do not use [Invented name] if you are pregnant unless your doctor considers it necessary. If you could get pregnant you must use adequate contraception whilst you use the medicine.

Do not use [Invented name] if you are breast-feeding. This medicine may get into your milk**.**

Driving and using machines
You may find that your vision is blurred for a time just after you use [Invented name]. Do not drive or use machines until this has worn off.

[Invented name] contains benzalkonium chloride
This medicine contains benzalkonium chloride, which may cause eye irritation.
Avoid contact with soft contact lenses.
Remove contact lenses prior to application and wait at least 15 minutes before reinsertion.
Known to discolour soft contact lenses.

[Invented name] contains macrogolglycerol hydroxystearate 40
This medicine contains macrogolglycerol hydroxystearate 40, which may cause skin reactions.

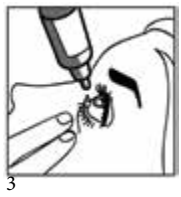
3. How to use [Invented name]

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is
One drop in the affected eye or eyes, once a day-in the morning or in the evening. Use at the same time each day.
Only use [Invented name] in both eyes if your doctor told you to do so. Use it for as long as your doctor told you to.

Only use [Invented name] for dropping in your eyes.

Instructions for use

 1	• Immediately before using a bottle for the first time, tear-off the sachet (picture1). Take out the bottle and write the date of opening on the label in the space provided. • Get the medicine bottle and a mirror. • Wash your hands.
 2	• Hold the bottle, pointing down, between your thumb and fingers. • Tilt your head back. Pull down your eyelid with a clean finger, until there is a 'pocket' between the eyelid and your eye. The drop will go in here (picture 2). • Bring the bottle tip close to the eye.Use the mirror if it helps.
 3	• **Do not** touch **your eye or eyelid, surrounding areas or other surfaces with the dropper.**It could infect the drops. • Gently squeeze the bottle to release one drop of medicine at a time **(picture 3)**eye.Use the mirror if it helps.
 4	• After using the medicine press a finger into the corner of your eye, by the nose **(picture4)**. This helps to stop the medicine getting into the rest of the body. • If you use drops in both eyes, repeat these same steps for your other eye. Close the bottle cap firmly immediately after use. Only use one bottle of medicine at a time. Do not open the sachet until you need to use the bottle. **You must throw away the bottle 4 weeks after you first opened it, to prevent infections, and use a new bottle.**

If a drop misses your eye, try again.

If you use more [Invented name] than you should
If you use more [Invented name] than you should, rinse it all out with warm water. Do not put in any more drops until it is time for your next regular dose.

If you forget to use [Invented name]
If you forget to use [Invented name], continue with the next dose as planned. Do not use a double dose to make up for a forgotten dose. The dose should not exceed one daily drop in the affected eye(s).

If you stop using [Invented name]
If you stop using [Invented name] without speaking to your doctor the pressure in your eye will not be controlled which could lead to loss of sight.

If you are using other eye drops, leave at least 5 minutes between putting in [Invented name] and the other drops.

If you wear soft contact lenses do not use the drops with your lenses in. After using the drops wait 15 minutes before putting your lenses back in.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

You can usually carry on taking the drops, unless the effects

are serious. If you're worried, talk to a doctor or pharmacist. Do not stop using [Invented name] without speaking to your doctor.

Very common (may affect more than 1 in 10 people):
Effects in the eye: eye redness

Common (may affect up to 1 in 10 people):
Effects in the eye: eye surface inflammation with surface damage, eye pain, blurred vision, abnormal vision, dry eye, itchy eye, eye discomfort, signs and symptoms of eye irritation (e.g. burning, stinging).

Uncommon (may affect up to 1 in 100 people):
Effects in the eye: inflammation of the eye surface, inflammation of the eyelid, swollen conjunctiva, increased growth of eyelashes, iris inflammation, eye inflammation, sensitivity to light, reduced vision, tired eyes, eye allergy, eye swelling, increased tear production, eyelid redness, eyelid colour change

General side effects: drug allergy, dizziness, headache, increased or decreased blood pressure, shortness of breath, excessive hair growth, drip at back of throat, skin inflammation and itching, decreased heart rate.

Rare side effects (may affect up to 1 in 1,000 people):
Effects in the eye: thinning of the eye surface, inflammation of the eyelid glands, broken blood vessel in the eye, eyelid crusting, abnormally positioned eyelashes, abnormal growth of lashes.

General side effects: nervousness, irregular heart rate, loss of hair, voice disorders, difficulty breathing, cough, throat irritation, hives, abnormal liver blood tests, skin discolouration, skin darkening, thirst, tiredness, discomfort inside of nose, coloured urine, pain in hands and feet.

Not known (frequency cannot be estimated from the available data):
Effects in the eye: droopy eyelid (making the eye stay half closed)

General side effects: rash, heart failure, chest pain, stroke, fainting, depression, asthma, increased heart rate, numbness or tingling sensation, palpitations, swelling in the lower limbs, bad taste.

Additionally:

[Invented name] is a combination of 2 active substances. Like other medicines applied into eyes, travoprost and timolol (a beta-blocker) are absorbed into the blood. This may cause similar side effects as seen with intraveneous and/or oral beta-blocking medicines. The incidence of side effects after topical ophthalmic administration is lower than when medicines are, for example, taken by mouth or injected. Listed side effects which include reactions seen within the class of beta-blockers when used for treating eye conditions are as follows:

Effects in the eye: inflammation of the eyelid, inflammation in the cornea, detachment of the layer below the retina that contains blood vessels following filtration surgery which may cause visual disturbances, decreased corneal sensitivity, corneal erosion (damage to the front layer of the eyeball), double vision, changes in the colour of the iris

General side effects:

- Heart and circulation: slow heart rate, palpitations, oedema (fluid build up),
  changes in the rhythm or speed of the heartbeat,
  congestive heart failure (heart disease with shortness of breath and swellin of the feet and legs due to fluid build up), a type of heart rhythm disorder, heart at tack low blood pressure,
  Raynaud's phenomenon, cold hands and feet, reduced blood supply to the brain.

- Respiratory: constriction of the airways in the lungs (predominantly in patients with pre-existing disease), difficulty breathing, stuffy nose

- Nervous system and general disorders: difficulty sleeping (insomnia), nightmares, memory loss loss of strength and energy

- Gastric: taste disturbances, nausea, indigestion, diar rhea, dry mouth, abdominal pain,
  vomiting

- Allergy: generalized allergic reactions including swelling beneath the skin that can occur in ar eas such as the face and limbs, and can obstruct the air way which may cause difficulty swallowing or breathing, localized and generalized rash, itchiness, severe sudden life-threatening allergic reaction.
- Skin: skin rash with white silvery coloured appearance (psoriasiform rash) or worsening of psoriasis, peeling skin
- Muscular: increases in signs and symptoms of myasthe nia gravis (muscle disorder), un usual sensations like pins and needles, muscle weakness / tiredness, muscle pain not caused by exercise.

- Reproduction: sexual dysfunction, decreased libido

- Metabolism: low blood sugar levels

Reporting of side effects
If you get any side effects, talk to your doctor or phar macist.This includes any possible side effects not listed in this leaflet.You can also report side effects directly via Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard
By reporting side effects you can help provide more in formation on the safety of this medicine.

5. How to store [Invented name]

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton and bottle after EXP. The expiry date refers to the last day of that month.
Before opening, keep the bottle in the sachet in order to protect from moisture. After first opening, this medicine does not require any special storage conditions.

You must throw away the bottle 4 weeks after you first opened it, to prevent infections, and use a new bottle. Write down the date you opened the bottle in the space the bottle label and box.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What [Invented name] contains

- The active substances are travoprost and timolol.
  Each mL of solution contains 40 micrograms of travoprost and 5 mg of timolol (as timolol maleate).
- The other ingredients are benzalkonium chloride solution 50% w/v, macrogolglycerol hydroxystearate (nom inal value:40), trometamol, edetate disodium, boric acid, mannitol, sodium hydroxide 5N and water for injection.

What [Invented name] looks like and contents of the pack
[Invented name] eye drops, solution is presented as a clear, colorles, aqueous solution supplied in containing [X] polypropylene vials of 5ml with white opaque LDPE nozzle and a white opaque HDPE/LDPE cap with tamper proof seal. Each bottle is enclosed in a sachet. Each bottle contains 2.5 ml solution.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

<[To be completed nationally]>

This leaflet was last revised in

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Appendix 3 - Protocol

PROTOCOL
Bridging Study for the Package Information Leaflet (PIL)

[Invented name] 40 micrograms/mL+ 5 mg/mL eye drops, solution

travoprost/timolol

Project contractor:		**ELC Group**	
Project name:		**Bridging Study**	
Project Manager on behalf of ELC:			
Version Number:	1.0	**Date:**	April 5, 2016

Rationale:

The objectives of the bridging study of the Daugher PIL by ELC Group is to ensure that the PIL is compliant with the European Council Directive 2004/27/EC which states: "The package leaflet shall reflect the results of consultation with target patient groups to ensure that it is legible, clear and easy to use". In performing this study it will be demonstrated that the Daughter PIL is similar to the Package Information Leaflet for the Parent PIL, and therefore requires no further user testing.

The basis for the report and its evaluation will be based on both European Commission (Article 59(3) of Council Directive 2001/83/EC and also by Article 63(2) of Directive 2001/83/EC as amended), the European Commission document “Guideline on the readability of the labelling and package leaflet of medicinal products for human use” (2009), Recommendations for Bridging from CMDh (April 2009, Revision 1) and MHRA guidance on bridging (Guidance for the Pharmaceutical Industry on the use of BRIDGING STUDIES to demonstrate compliance with article 59(3) of Council Directive 2001/83/EC [Consultation with Target Patient Groups]), as well as specific information and feedback obtained by ELC Group from the relevant authorities on the use of bridging in user testing schemes.

Background:

Daughter PIL

Travoprost/Timolol eye drops solution is a combination of two active substances (travoprost and timolol). Travoprost is a prostaglandin analogue which works by increasing the outflow of liquid of the eye, which lowers its pressure. Timolol is a beta blocker which works by reducing the production of fluid within the eye. The two substances work together to reduce pressure within the eye.

Travoprost/Timolol eye drops are used to treat high pressure in the eye in adults, including the elderly**.** This pressure can lead to an illness called glaucoma.
Travoprost/Timolol eye drops solution is a sterile solution that does not contain a preservative.

Parent PIL

Travoprost/Timolol eye drops solution is a combination of two active substances (travoprost and timolol). Travoprost is a prostaglandin analogue which works by increasing the outflow of liquid of the eye, which lowers its pressure. Timolol is a beta blocker which works by reducing the production of fluid within the eye. The two substances work together to reduce pressure within the eye.

Travoprost/Timolol eye drops are used to treat high pressure in the eye in adults, including the elderly**.** This pressure can lead to an illness called glaucoma.

Study design:

The PIL proposed for bridging will be evaluated and compared to the previously approved PIL using the following criteria:

- **Layout and Style**: size, font, colors, and organization of sections.
- **Contents**: indications, contraindications, side effects, ingredients, storage information, and any other relevant data. Key safety messages of the Parent PIL have been successfully user tested; the key safety messages of the Daughter PIL are to be identical or very similar.

Once the PIL proposed for bridging is compared, differences between the PILs will be analyzed.

Responsibilities:

Sponsor

- Provide source documents

Contractor

- An assessment of PILs to determine if a bridging study is warranted.
- Comparison of the PIL proposed for bridging to the previously approved PIL.
- Analyses and reporting of differences.
- Delivery of the final report: a full report of testing ready for submission to regulatory authority in Europe, which shall include the results of the assessment carried out and PIL drafts annotated to show proposed amendments (if applicable).

Project Milestones:

Milestone
Receive source documents from client
Initial evaluation of Daughter PIL
Comparison of the Daughter PIL to the proposed Parent PIL
Preparation of a mock-up of the Daughter PIL, harmonised to the Parent PIL
Evaluation of differences between the Daughter and Parent PIL
Creation of the Final Report
Delivery of the final report and raw data to the sponsor