Elements for a Public Summary

MONOCOM is a preservative free eye drop solution that contains the active substances latanoprost and timolol.

VI.2.1 Overview of disease epidemiology

MONOCOM is 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(s), eventually affecting your eye sight.

By the year 2020, it has been estimated that there will be about 59 million people with open angle glaucoma. Risk factors for open-angle glaucoma include increased age, African ethnicity, family history, increased pressure inside the eye, myopia, and decreased corneal thickness (the cornea is the transparent layer in front of the eye that covers the pupil and iris).

Bilateral blindness (blindness in both eyes) from glaucoma has been projected to affect more than 11 million people worldwide by 2020.

Latanoprost belongs *to* a group of medicines known as prostaglandins. It lowers the pressure within your eye by increasing the natural outflow of fluid from inside the eye into the bloodstream.

Timolol belongs to a group of medicines called “beta-blockers”, it works by slowing the formation of fluid in the eye.

When intraocular pressure is raised, it causes damage to the retina (the light-sensitive membrane at the back of the eye) and to the optic nerve that sends signals from the eye to the brain. This can result in serious vision loss and even blindness. By lowering the pressure, MONOCOM reduces the risk of damage.

The medicine can only be obtained with a prescription.

The dose is one drop of MONOCOM in the affected eye(s) once a day.

VI.2.2 Summary of treatment benefits

For the treatment of glaucoma, several options as an initial intervention are available, namely surgical, laser or medical. Medical management is the general standard of practice for the initial treatment of open-angle glaucoma.

Several different medicinal products can be used in the treatment of glaucoma. However, the introduction of prostaglandin analogs (PGAs) like latanoprost significantly changed the treatment practice of glaucoma. The benefit of IOP reduction in the treatment of glaucoma has been confirmed in large clinical trials, and PGAs are considered the first line treatment for IOP. Although prostaglandins are highly effective IOP-reducing agents in a number of patients, combined treatment with two or many drugs is sometimes needed for adequate control of increased intraocular pressure. Other useful medications are β-adrenergic antagonists (e.g. timolol), cholinergic agonists (e.g. pilocarpine), α-adrenergic agonists (e.g. brimonidine) or carbonic anhydrase inhibitors (e.g.dorzolamide, brinzolamide).

The most frequently used combination of prostaglandins is with the beta-blocking agent timolol. There are several prostaglandin-timolol combination products on the market. The advantage of combination products is that the treatment regimen becomes simpler for the patient thereby improving the compliance with better intraocular pressure control.

The latanoprost-timolol combination is indicated for the reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension.

The company provided data from the published literature on Latanoprost and Timolol Reference Product (XALACOM) already authorised in the European Union (EU), and from other marketed products that contain respectively Latanoprost and Timolol (Monoprost, Duokopt).

Moreover, Monocom (Latanoprost and Timolol) were evaluated in 242 adults with ocular hypertension or open angle glaucoma, confirmed being insufficiently controlled on monotherapy. In these studies, Monocom was compared with the preserved 0.005% latanoprost and timolol reference product (XALACOM).

- LT2347-PIII-12/13 – 242 patients - duration 6 weeks

The efficacy and tolerability of the latanoprost/timolol fixed combination for the management of Open Angle Glaucoma and Ocular Hypertension remains undisputed, and the extensive data, including the results of Study 12/13 conducted by the Applicant, support its use as second-line treatment in patients insufficiently responsive to topical beta-blockers or prostaglandin analogs.

Based on these data, the Applicant considers that the proposed medicinal product has a positive benefit/risk profile, with an advantage over the currently marketed reference product in terms of ocular tolerability/safety on a long-term.

In addition, the safety and efficacy of latanoprost and/or timolol in adult patients with elevated eye pressure is supported by more than one decade of clinical experience. The latanoprost-timolol combination therapy is an effective intra-ocular pressure reducing medicine. The combination was more effective than latanoprost or timolol given as monotherapy, and at least as effective as latanoprost and timolol given concomitantly.

VI.2.3 Unknowns relating to treatment benefits

Overall, the patients enrolled in clinical trials represent the population that would expect to receive MONOCOM, with the exception of children, pregnant women or nursing mothers, patients with hepatic and renal impairment, patients with advanced glaucoma, patients who have been operated for cataracts, patients with a history of active intraocular inflammation and/or with active intraocular disease.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergic reaction (Hypersensitivity)	Allergy induced by topical glaucoma treatment is primarily seen in the conjunctiva and around the eye. Serious allergic reactions to latanoprost and timolol are rare.	Yes, by avoiding use of latanoprost and timolol and/or in patients with hypersensitivity to latanoprost, timolol or to any of the excipients, or with a tendency to develop allergies and asthma. Also by monitoring for early symptoms.

Risk	What is known	Preventability
Redness of the eye	During the development of Monocom, some cases of redness of eyes were reported upon instillation. These reactions were mild and transient. Frequency: uncommon	In the leaflet, the patient is informed that redness of the eye may affect up to 1 in 100 people and that in case the patient used more Monocom than he should, he may experience some minor irritation in his eye. The patient is advised this should pass but if he is worried to contact his doctor for advice.
Change in eye colour **Hyperpigmentation (darkening around the eye)**	Iris darkening (frequency ≥1/10) and skin darkening around the eyes (frequency >1/100 to <1/10) have been reported with latanoprost. They do not pose a known threat to vision or health. Skin changes seem to be reversible after discontinuation of the medicine. However, iris darkening is often irreversible.	The risk of iris darkening appears to depend on eye colour before treatment. Patients with non-homogenously blue, grey or hazel irises show greater changes. Caution should be exercised when treating glaucoma only in one eye with prostaglandin analogs (class of medicines to which latanoprost belongs).
Eye lash and vellus hair changes	Excessive growth of hair is considered as a non-serious and mild effect associated with the use of prostaglandin analogs.	The effects of latanoprost or any other prostaglandin on the periocular skin and the eyelashes can be minimised by reducing skin-eye drop contact as best as possible in the daily dosing scheme. Termination of prostaglandin analog treatment may reverse this effect but conclusive evidence has not been obtained. Patients who have abnormally positioned eyelashes that grow back toward the eye should be monitored for this complication.
Increased risk of swelling of the retina (cystoid macular oedema)	Macular oedema has been reported during treatment with Latanoprost and other products from the same class. This effect is usually reversible after discontinuation of the medicine.	Yes, by avoiding use of Latanoprost in patients who have undergone cataract surgery or other ocular surgery as well as patients with other risk factors for macular oedema, such as ocular (eye)

Risk	What is known	Preventability
		inflammations, diabetes or hypertension (high blood pressure). If Latanoprost is used in such patients, patients should check their vision frequently and promptly report any change. In case of macular oedema, the medicine should not be used again, to prevent recurrence.
Bronchospasm	Bronchospasm occurred predominantly in patients with pre-existing bronchospastic disease. Serious respiratory ADRs are possible and in rare cases life-threatening. Concomitant beta-blockers or other antiadrenergic drugs could potentiate the effects of timolol. The overall risk is expected be lower with topical beta-blockers compared with systemic betablockers.	Yes, by avoiding use of Latanoprost and Timolol in patients with pre-existing respiratory disorders.
Aggravation of asthma	Respiratory disorders such as dyspnoea (difficulty breathing), asthma and worsening of asthma have been associated with the use of prostaglandin analogs. These and other respiratory symptoms have been reported with the use of Latanoprost.	Yes, by avoiding use of Latanoprost and Timolol in patients with pre-existing respiratory disorders.
Bradycardia	Cardiac disorders such as angina pectoris (pains to the chest, jaw and back), bradycardia (slow heart rate), chest pain have been reported in association with Latanoprost administration although they are considered very rare. Beta-blockers can worsen the cardiac disorders. Serious cardiac ADRs are possible and in rare cases life-threatening. Pre-existing disease, other beta-blockers or antiadrenergic drugs increases the risk. The overall risk is expected be lower with topical beta-blockers compared with systemic beta-blockers.	Yes, by avoiding use of Latanoprost and timolol in patients with pre-existing cardiovascular disorders.

Important Potential Risk

Risk	What is known
Melanoma (pigmented skin cancer)	Prostaglandin analogs are well known to cause pigmentary (colour) changes in iris, eyelashes and skin around the eye. The mechanism by which they increase pigment synthesis is uncertain. Melanoma was not seen in the clinical trials for latanoprost which studied 462 patients and healthy volunteers. Four cases have been reported in the literature with latanoprost or a member of the same pharmaceutical class: one choroidal melanoma and two cutaneous melanomas associated with latanoprost and one eyelid melanoma associated with bimatoprost (another type of prostaglandin analog). However, a direct link between prostaglandin analog use and development of melanoma has never been documented.

Missing information

Risk	What is known
Use in paediatric population	During the development of Monocom, patients under the age of 18 years have been excluded from participation in clinical trials. Thus, the safety and efficacy of Monocom in children and adolescents have not been established and its use is not recommended in these patients until further data become available.
Drug interactions	The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is given to the patients already receiving a systemic beta-blocking agent. There is a potential for additive effects resulting in hypotension and/or marked bradycardia when an ophthalmic beta-blockers solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, or guanethidine. Prostaglandin analogs, when not used adequately, e.g. not exactly as described in the leaflet or as your doctor told you, may have reduced efficacy. For example, a higher daily dosing regimen or the association with another prostaglandin analog may reduce the efficacy of latanoprost.

Use during pregnancy and lactation	Pregnancy *Latanoprost* There are no adequate data from the use of latanoprost in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. *Timolol* There are no adequate data for the use of timolol in pregnant women. Timolol should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see section 4.2. Epidemiological studies have not revealed malformative effects but show a risk for intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If is administered until delivery, the neonate should be carefully monitored during the first days of life. Consequently should not be used during pregnancy. Breast-feeding Beta-blockers are excreted in breast milk. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant. To reduce the systemic absorption, see section 4.2. Latanoprost and its metabolites may pass into breast milk. Monocom should therefore not be used in women who are breast feeding.
Long-term ocular safety (due to the presence of macrogolglycerol hydroxystearate (derived from castor oil)	MONOCOM contains macrogolglycerol hydroxystearate (derived from castor oil) which may cause delayed ocular reaction. No long-term safety data in humans are currently available on this excipient. Therefore, close surveillance of delayed ocular reaction will be performed.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimization measures.

The Summary of Product Characteristics and the Package leaflet for MONOCOM can be found in the Competent Authority web-page.

This medicine has no additional risk minimization measures.

VI.2.6 Planned post authorisation development plan

Laboratoires Thea is not planning to perform post-authorisation studies at the moment.

VI.2.7 Summary of changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	15 Sept. 2016	**Important identified risks** • Hypersensitivity reactions • Respiratory reactions • Cardiovascular disorders • Increased pigmentation of iris • Periocular skin pigmentation • Hypertrichosis • Increased risk of macular oedema including cystoid macular oedema • Increased risk of iritis/uveitis • Increased risk of recurrence or flare-up of herpetic keratitis • Choroidal detachment • Concomitant treatment with systemic beta-blocking agents • Hypoglycaemia, diabetes **Important potential risks** • Local overdose with latanoprost and/or concomitant treatment with another Prostaglandin analog • Use during pregnancy or lactation • Use in paediatric population • Melanoma of the eye and skin • Use for cosmetic purposes as eye lashes enhancer or for alopecia (hypertrichosis) Hypertension **Missing information** • Long-term ocular safety (due to the high concentration of	First version of the RMP

Version	Date	Safety Concerns	Comment
		macrogolglycerol hydroxystearate) • Use in patient with hepatic impairment • Use in patient with renal impairment	
2.0	15 May 2017	**Important identified risks** • Hypersensitivity reactions • Conjunctival hyperaemia • Bronchospasm • Aggravation of asthma • Bradycardia • Increased pigmentation of iris • Periocular skin pigmentation • Eye lash and vellus hair changes • Cystoid macular oedema **Important potential risks** • Melanoma of the eye and skin **Missing information** • Paediatric patients • Drug interactions • Pregnant and lactating women • Long-term ocular safety (due to the high concentration of macrogolglycerol hydroxystearate)	Change of the risks to be in line with Xalacom
2.1	19 Mar. 2018	**Important identified risks** • Hypersensitivity reactions • Conjunctival hyperaemia • Bronchospasm • Aggravation of asthma • Bradycardia • Increased pigmentation of iris • Periocular skin pigmentation • Eye lash and vellus hair changes • Cystoid macular oedema **Important potential risks** • Melanoma of the eye and skin **Missing information** • Paediatric patients	Update to be in line with the new proposed SPC and PIL

Version	Date	Safety Concerns	Comment
		• Drug interactions • Pregnant and lactating women • Long-term ocular safety (due to the high concentration of macrogolglycerol hydroxystearate)	