IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This application for a marketing authorisation was made under article 10(3) of Directive 2001/83/EC as amended. Timlatan 50 micrograms/ml + 5 mg/ml eye drops solution is a generic version of the already approved reference product Xalacom by Pfizer, which has been marketed in the EU for more than 6 years.

Background disease

Glaucoma is one of the leading causes of irreversible blindness worldwide, and treatment is aimed at reducing levels of intraocular pressure (IOP) using ocular hypotensive agents. Patients often need more than one class of IOP reducing medication, and this can result in complex regimens which are difficult to maintain and can lead to non-compliance. Combination medicinal products can be helpful in reducing this complexity and improving compliance. Timlatan 50 micrograms/ml + 5 mg/ml eye drops solution contains two active substances, namely, latanoprost and timolol maleate.

II. QUALITY ASPECTS

II.1 Introduction

This application is for a latanoprost/timolol 50 micrograms/ml + 5 mg/ml eye drops solution.

II.2 Drug Substance

Latanoprost
The drug substance, latanoprost, is a well established active substance. It is not described in the European Pharmacopoeia (Ph.Eur.).

Synthesis of the drug substance has been satisfactorily described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis. Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient.

The active substance specifications are considered adequate to control the quality and meet current requirements. Batch analytical data demonstrating compliance with this specification have been provided for representative batches.

The container is suitable and provides adequate protection to the active substance.

Based on stability data presented, an appropriate re-test period has been set.

Timolol Maleate
The drug substance, timolol maleate, is a well established active substance which is monographed in the European Pharmacopoeia (Ph.Eur.). The EDQM Certificate of Suitability (CEP) procedure is used and the CEP is presented in the documentation.

The active substance specification is considered adequate to control the quality and meets the current requirements of the Ph. Eur. monograph for Timolol maleate and additional requirements as stated on the CEP. Batch analytical data demonstrating compliance with this specification have been provided for three representative batches.

An appropriate re-test period has been set.

II.3 Medicinal Product

II.3.1 Composition

The drug product is presented as a sterile, preserved, isotonic, multidose clear and colorless ophthalmic solution containing 50 microgram/ml of latanoprost and 6.8 mg/ml timolol maleate (equivalent to 5 mg/ml timolol) as active substances. It also contains the preservative benzalkonium chloride. The product is packaged in bottles made of Low Density Polyethylene (LDPE) containing 2.5 ml of drug product and equipped with a dropper applicator and a High Density Polyethylene (HDPE) screw cap.

II.3.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The purpose of the development was to develop a stable product essentially similar to the reference product, Xalacom. Comparative analysis with the reference product on the EEA market has demonstrated essential similarity.

II.3.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP). The product is manufactured using conventional manufacturing techniques which have been validated using full scale batches. The results show good production performance throughout production. All tests meet the requirements in the finished product specification and the data demonstrate reproducibility of the manufacturing process.

II.3.4 Control of Excipients

All excipients comply with their respective European Pharmacopoeia monographs. There are no excipients of human or animal origin used in the manufacture of the product. There are no novel excipients used in the manufacture of the product.

II.3.5 Control of Finished Product

The finished product specification is adequate to control the relevant parameters for the dosage form. The release specifications for the drug product are based on the relevant European guidelines and the standard requirements associated with eye preparations. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

II.3.6 Packaging Material

The product is packaged in bottles made of Low Density Polyethylene (LDPE) containing 2.5 ml of drug product and equipped with a dropper applicator and a High Density Polyethylene (HDPE) screw cap. HDPE/LDPE bottles are widely used for this type of product. Bottle drawings and test certificates are provided. The packaging material complies with the relevant European guidelines.

II.3.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product. The approved shelf life of the product as packaged for sale and the storage conditions are stated in the Summary of Product Characteristics (SPC). Once open the product should be used within 4 weeks (see the SPC for further information).

II.4 Discussion on chemical, pharmaceutical and biological aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality ofTimlatan 50 micrograms/ml + 5 mg/ml eye drops solution.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This application for Timlatan 50 micrograms/ml + 5 mg/ml eye drops solution**is submitted pursuant to Article 10 (3) of Directive 2001/83/EC as amended. This is the appropriate legal basis for topical products for which bioequivalence**

cannot be demonstrated through bioavailability studies. Timlatan 50 micrograms/ml + 5 mg/ml eye drops solution**is proposed as a hybrid medicinal product.**
The active components of Timlatan 50 micrograms/ml + 5 mg/ml eye drops solution,latanoprost and timolol maleate, have each been approved as first line therapeutic agents for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension in the EU. Latanoprost active substance belongs to the F2a prostaglandin analogues. This agent acts by increasing the outflow of aqueous humour, primarily through the uveoscleral pathway. The individual active substance of timolol maleate is a non selective beta-adrenergic receptor blocker and induces reduction of IOP by decreasing the formation of aqueous humour. No clinical studies were carried out in order to demonstrate bioequivalence between Timlatan 50 micrograms/ml + 5 mg/ml eye drops solutionand the originator product Xalacom.

This medicinal product has a similar composition to medicinal products already existing on the European market for many years and the product is intended to be a substitute for identical products on the market. The pharmacodynamic, pharmacokinetic and toxicological properties of latanoprost and timolol are well known. As both latanoprost and timolol are widely used, well known active substances that have previously been extensively used in combination, the applicant has not provided additional studies and further studies are not required. The non-clinical overview based on literature review is, considered appropriate. The active principles used for the manufacturing of the proposed medicinal product Timlatan 50 micrograms/ml + 5 mg/ml eye drops solution, were introduced in 1996 in the US and Europe.
The expert report is considered appropriate and sufficient to perform the review, as set out in Article 12 and in accordance with Annex I, Part I 1.4 of the Directive 2001/83/EC. The non-clinical overview combines and summaries of the published literature, both non-clinical and clinical, and provides an extensive overview of current knowledge with respect to local effects on the eye as well as systemic effects following alternative routes of administration.

Sections 4.6 and 5.3 of the SPC are in line with the originator product and are considered to be appropriate.

The present application is made under article 10(3) of Directive 2001/83/EC as amended, i.e.
Timlatan 50 micrograms/ml + 5 mg/ml eye drops solutionis a generic version of the already approved reference product Xalacom by Pfizer, which has been marketed in the EU for more than 6 years. No environmental risk assessment has been provided and this is in accordance with "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" CHMP/SWP/4447/00

III.2 Discussion on the non-clinical aspects

The medicinal product has a similar composition to medicinal products already existing on the European market for many years and the product is intended to be a substitute for identical products on the market for which there is extensive pre-clinical and clinical experience. No further testing is required with respect to pre-clinical or ecotoxicology.

IV. CLINICAL ASPECTS

IV.1 Introduction

Timlatan 50 micrograms/ml + 5 mg/ml eye drops solutionwere developed by S.C. Rompharm Company S.R.L., Romania, as generic equivalents to the European brands (Xalacom, Xalcom and Tavu respectively) of Pfizer and affiliates.

The first marketing authorisation for Xalacom 50 micrograms/ml + 5 mg/ml eye drops solutionin the EU has been granted on December 15, 2000 in Sweden.

Consequently, six years have passed since the first approval of Xalacom 50 micrograms/ml + 5 mg/ml eye drops solutionin a member state of the European Union, and reference can be made to preclinical and clinical documentation of the innovator.

Timlatan 50 micrograms/ml + 5 mg/ml eye drops solutionis essentially similar to Xalacom which is approved and marketed in Sweden as well as in all other countries in the EEA. Timlatan 50 micrograms/ml + 5 mg/ml eye drops solutionis of the same type of aqueous solution and contains the same concentration of the same active substances.

The excipients for Timlatan 50 micrograms/ml + 5 mg/ml eye drops solutionwere selected based on the composition of the original product Xalacom and with respect to the requirements for ophthalmic preparations.

<u>Therapeutic Indication</u>

Reduction of intraocular pressure (IOP) in patients with open angle glaucoma and ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues

IV.2 Pharmacokinetics

Latanoprost

Latanoprost is an isopropyl ester pro-drug, which *per se* is inactive, but after hydrolysis by esterases in the cornea to the acid of latanoprost, becomes biologically active. The pro-drug 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 maximum concentration in the aqueous humour, approximately 15-30 ng/ml, is reached about 2 hours after topical administration of latanoprost alone. After topical application in monkeys latanoprost is distributed primarily in the anterior segment, the conjunctiva and the eyelids.

The acid of latanoprost has a plasma clearance of 0.40 l/h/kg and a small volume of distribution, 0.16 l/kg, resulting in a rapid half life in plasma, 17 minutes. After topical ocular administration the systemic bioavailability of the acid of latanoprost is 45%. The acid of latanoprost has a plasma protein binding of 87%.

There is practically no metabolism of the acid of latanoprost in the eye. The main metabolism occurs in the liver. 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.

Timolol

The maximum concentration of timolol in the aqueous humor is reached about 1 hour after topical administration of eye drops. Part of the dose is absorbed systemically and a maximum plasma concentration of 1 ng/ml is reached 10-20 minutes after topical administration of one eye drop to each eye once daily (300 micrograms/day). The half life of timolol in plasma is about 6 hours. Timolol is extensively metabolised in the liver. The metabolites are excreted in the urine together with some unchanged timolol.

Latanoprost/Timolol

No pharmacokinetic interactions between latanoprost and timolol were observed although there was an approximate 2-fold increased concentration of the acid of latanoprost in aqueous humour 1-4 hours after administration of latanoprost/timolol compared to monotherapy.

IV.3 Pharmacodynamics

Pharmacotherapeutic group: Ophthalmological-betablocking agents - timolol, combinations ATC code: S01ED51

Mechanism of action

Timlatan 50 micrograms/ml + 5 mg/ml eye drops solution consists of two components: latanoprost and timolol maleate. These two components decrease elevated intraocular pressure (IOP) by different mechanisms of action and the combined effect results in additional IOP reduction compared to either compound administered alone.

Latanoprost, a prostaglandin F_{2alpha} analogue, is a selective prostanoid FP receptor agonist that reduces the IOP by increasing the outflow of aqueous humour. The main mechanism of action is increased uveoscleral outflow. Additionally, some increase in outflow facility (decrease in trabecular outflow resistance) has been reported in man. Latanoprost has no significant effect on the production of aqueous humour, the blood-aqueous barrier or the intraocular blood circulation. 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.

Timolol is a beta-1 and beta-2 (non-selective) adrenergic receptor blocking agent that has no significant intrinsic sympathomimetic, direct myocardial depressant or membrane-stabilising activity. Timolol lowers IOP by decreasing the formation of aqueous in the ciliary epithelium. The precise mechanism of action is not clearly established, but inhibition of the increased cyclic AMP synthesis caused by endogenous beta-adrenergic stimulation is probable. Timolol has not been found to

significantly affect the permeability of the blood-aqueous barrier to plasma proteins. In rabbits, timolol was without effect on the regional ocular blood flow after chronic treatment.

Pharmacodynamic effects

Clinical effects

In dose finding studies, latanoprost/timolol produced significantly greater decreases in mean diurnal IOP compared to latanoprost and timolol administered once daily as monotherapy. In two well controlled, double masked six-month clinical studies the IOP reducing effect of latanoprost/timolol was compared with latanoprost and timolol monotherapy in patients with an IOP of at least 25 mm Hg or greater. Following a 2-4 week run-in with timolol (mean decrease in IOP from enrolment of 5 mm Hg), additional decreases in mean diurnal IOP of 3.1, 2.0 and 0.6 mm Hg were observed after 6 months of treatment for latanoprost and timolol (twice daily), respectively. The IOP lowering effect of latanoprost/timolol was maintained in 6 month open label extensions of these studies.

Existing data suggest that evening dosing may be more effective in IOP lowering than morning dosing. However, when considering a recommendation of either morning or evening dosing, sufficient consideration should be given to the lifestyle of the patient and their likely compliance.

It should be kept in mind that in case of insufficient efficacy of the fixed combination, results from studies indicate that the use of unfixed administration of timolol twice daily and latanoprost once a day might be still efficient.

Onset of action of latanoprost/timolol is within one hour and maximal effect occurs within six to eight hours. Adequate IOP reducing effect has been shown to be present up to 24 hours post dosage after multiple treatments.

IV.4 Clinical efficacy

The clinical efficacy of this fixed-combination product has been well established for the innovator Xalacom which is approved and marketed in Ireland as well as in all other countries in the EEA. As this is a generic formulation and is deemed to be bioequivalent with the reference no difference in efficacy is expected.

IV.5 Clinical safety

The clinical safety of this combination product is well established. The product has been authorised and marketed in the European Union since 2000.The most common adverse event associated with latanoprost is iris pigmentation, and this is more common in persons with mixed-colour irides, such as green-brown or yellow, brown. Iris pigmentation occurs very commonly, and while it generally occurs after prolonged use, it can occur after only a few months use. While there are no apparent adverse clinical effects of this hyper-pigmentation, it can be irreversible. Conjunctival and scleral hyperemia is also commonly observed. Latanoprost is not recommended in patients who have had ocular surgery.

As timolol is absorbed into the systemic circulation, it can cause adverse events in a similar way to other beta-adrenergic blocking agents. Patients with concomitant respiratory, cardiac, or endocrine diseases are generally advised to use beta-blockers with caution.

Pharmacovigilance System

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided

Risk Management Plan

An EU-RMP was not considered necessary at this time – routine pharmacovigilance was deemed sufficient.

IV.6 Discussion on the clinical aspects

Additional clinical efficacy or safety studies are not necessary as this formulation is abridged to the innovator Xalacom.

V. OVERALL CONCLUSIONS

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Timlatan 50 micrograms/ml + 5 mg/ml eye drops solutionin the treatment of *Reduction of intraocular pressure (IOP) in patients with open angle glaucoma and ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues* was approvable as the benefit/risk profile is positive and therefore recommended granting a marketing authorisation.

VI. REVISION DATE

September 2021

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
MA transfer	CRN00CK31	SmPC section 7, 8, 10 Package Leaflet New MA Holder: Bausch + Lomb Ireland Limited New PA number: PA23259/001/001	N/A	10/09/2021