LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Fixopost
(latanoprost and timolol maleate)

SE/H/1602/002/DC
2019-0043

This module reflects the scientific discussion for the approval of Fixopost. The procedure was finalised on 2020-11-18. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Laboratoires Theá has applied for a marketing authorisation for Fixopost, 50 micrograms/ml + 5 mg/ml eye drops, solution (SE/H/1602/002/DC). The active substances latanoprost and timolol maleate are the same as in Fixopost eye drops, solution in single-dose container, marketed by Laboratoires Theá since 2018. The Marketing Authorisation for Fixopost eye drops, solution in single-dose container was granted to Laboratoires Théa through a Decentralised Procedure (SE/H/1602/001/DC), with Sweden acting as Reference Member State, in 28 European countries and positively ended on 2018-04-26 (International Birth Date).

Fixopost, 50 micrograms/ml + 5 mg/ml eye drops, solution is a line extension of Fixopost eye drops, solution in single-dose container.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Introduction

To support this application, the applicant has submitted three non-clinical studies to compare the efficacy, the pharmacokinetic profile and the local ocular tolerance of the unpreserved Fixopost formulation to the reference product Xalacom.. These studies were previously submitted to support Fixopost containing latanoprost 0.005% and timolol maleate 0.5% in single dose units.

In addition, a 28-day ocular tolerance study following twice daily instillations of a formulation with one of the active ingredients only (latanoprost) in the new multi-dose container or Xalatan was performed in albino rabbits. Studies on the primary packaging only was also carried out in order to ensure safety of the multi-dose container.

A non-clinical review of published relevant literature on the pharmacology, pharmacokinetics and toxicology of the active substances has also been provided.

III.2 Pharmacology

An appropriate review of published literature has been provided.

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.

Very few non-clinical studies related to the indication of the 0.005% latanoprost / 0.5% timolol combination were published. However, the primary pharmacodynamic effect of latanoprost and timolol is well documented in animals.

One study was performed to evaluate the ability of the unpreserved Fixopost formulation to reduce IOP in normotensive African green monkeys following topical delivery, in comparison with the reference product Xalacom. Both treatments resulted in a significant decrease of IOP in normotensive African green monkeys. The similarity in IOP changes induced with both treatments reflects the use of identical active substances, latanoprost and timolol. No adverse systemic or ocular events were reported following topical administration

III.3 Pharmacokinetics

The pharmacokinetic profile of latanoprost demonstrates adequate penetration of latanoprost acid into various ocular tissues of the anterior part of the eye. Systemic absorption of latanoprost acid is followed by a significant first-pass effect while the elimination from the plasma proceeds rapidly with an elimination half-life of approximately 10 min. Metabolites recovered from the urine and faeces of several animals include the 1,2 dinor acid of latanoprost and the tetranor metabolite which both result from β-oxidation of the acid of latanoprost.

Timolol is well absorbed orally and has a plasma half life of 30 and 60 minutes respectively in the rat and in the dog (about 4 hours in man). Timolol undergoes moderate first-pass metabolism, and is metabolized extensively by the liver; only a small amount of unchanged drug is excreted in the urine. After ocular administration of timolol, typically less than 5% of the drug penetrates the cornea and reaches intraocular tissues. The remainder enters the systemic circulation via absorption into the conjunctivae and drainage into the nasal cavity. In addition, the corneal epithelial cell barrier serves as an impedance to drug absorption into the eye. Peak systemic absorption of timolol maleate (0.5 mg/eye) occurred at 0.5 to 1.5 hours after ocular administration in man and produced peak blood plasma levels of 2 to 5 ng/mL.

From a safety point of view, the molecule with potential sytemic adverse effects in the combination, is timolol. Therefore, timolol was used as the pharmacokinetic tracer of the latanoprost/timolol fixed-combination in a pharmacokinetic study performed by the applicant. The aim of this study was to compare the plasma concentrations of timolol following once daily 25-µL instillations for 14 days in both eyes of pigmented rabbits of the unpreserved Fixopost formulation and the reference product Xalacom. Following once daily instillation for 14 days in both eyes, the concentration of timolol in plasma increased up to 1h and decreased thereafter (applicable to both formulations). No timolol was found in plasma at the residual time (24 h after the 13th day-instillation), these results were similar to those at 24 h after the last instillation. Based on $AUC_{0\text{-}24h}$ and the timolol plasma concentration the formulations were similar.

III.4 Toxicology

Non-clinical toxicology studies reported in the literature with the fixed combination are limited. However, the safety of both components latanoprost and timolol is well documented in both animals and humans.

The acute toxicity of latanoprost administered by topical eye route is low in animals. Long term treatments showed that the drug is well tolerated at doses which correspond to levels of exposure several hundred times than expected in humans. Latanoprost was neither mutagenic *in vitro* and *in vivo*, nor carcinogenic in mice and rats. Intravenously administered, latanoprost was not teratogenic in rats and in rabbits at doses corresponding to systemic exposure levels hundred times higher than in humans. However at such a level of exposure (approximately 100 times the expected level of exposure in humans), latanoprost was embryotoxic in the rabbit but not in the rat.

The ocular as well as systemic toxicity of latanoprost investigated in several animal species showed that this product is well tolerated. No toxic effects have been detected at doses up to 100 µg/eye/day in rabbits or monkeys (clinical dose is approximately 1.5 µg/eye/day). In monkeys, however, latanoprost has been shown to induce increased pigmentation of the iris.

Available documentation showed no evidence of timolol having any significant correlation between the β-antagonistic activity and chronic toxicity. Reproduction toxicity studies have shown that timolol has no effects on fertility and general reproductive performance, and no teratogenic potential. No

mutagenic potential of timolol was revealed, when tested in a standard battery of in vitro and in vivo genetic toxicology studies. No evidence of carcinogenicity was observed in rodents after oral doses of timolol, resulting in systemic exposures at least 7000 times higher than those in humans at topical therapy.

These experimental animal data are supported by more than 15 years of clinical experience of these two active substances separately or in a fixed combination all over the world. The safety profile of ocular latanoprost/timolol combination allows for a sufficient safety margin related to ocular administration.

The applicant has conducted a 28-day ocular tolerance study to compare the ocular tolerance of the unpreserved Fixopost formulation to that of the reference product Xalacom preserved eye drops after twice daily instillations for 28 days in the right eyes of albino rabbits. The unpreserved Fixopost test formulation was macroscopically and microscopically well tolerated, as was Xalacom.

III.5 Ecotoxicity/environmental risk assessment

The $PEC_{surfacewater}$ for latanoprost and timolol calculated according to CPMP/SWP/4447/00 are lower than the trigger value of 0.01 µg/L for both active ingredients; 0.000015 and 0.0015 µg/L respectively.

At pH 7, the logarithmic partition coefficients log Pow, determined by the applicant, are respectively 4.2 for latanoprost and -0.6 for timolol. As the log Pow value for latanoprost is above 3, a bioaccumulation study should be considered. However, based on the low $PEC_{surfacewater}$ value, further PBT assessment is not required.

- Considering the above data, latanoprost and timolol are not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

To support this application, the applicant has submitted one original clinical study developed to compare Fixopost to the originator Xalacom, including a review of published relevant literature (clinical pharmacology, clinical efficacy and clinical safety).

IV.2 Pharmacokinetics

No pharmacokinetic study was performed by the applicant in humans since the systemic exposure is expected to be similar to the reference product based on preclinical data in rabbits. Although the compounds included in the fixed dose combinations (FDC) are well-known, the formulation is considerably different compared to that of the reference product. This may have an impact on the systemic exposure. A non-clinical pharmacokinetic study showed timolol plasma exposure (C_{max} and AUC) was similar following multiple instillations (once a day for 2 weeks) of Fixopost and Xalacom in both eyes of pigmented rabbits. This is considered acceptable.

IV.3 Pharmacodynamics

No new data have been provided. Pharmacodynamics is appropriately described in the product information.

IV.4 Clinical efficacy

An appropriate review of published literature has been provided. The combination latanoprost+timolol is well known to have a relevant IOP lowering effect and used in treatment of glaucoma in patients insufficiently responsive to topical beta-blockers or prostaglandin analogues. The current application concerns a preservative free fixed dose combination (FDC) of latanoprost+timolol and the same formulation is already approved in a mono-composition of latanoprost (Monoprost).

One study (LT2347-PIII-12/13) was submitted for this hybrid application of a preservative free single dose fixed dose combination of latanoprost +timolol, Fixopost, to establish a bridge to the reference product Xalacom, thereby allowing for a conclusion about therapeutic similarity.

This study had previously been submitted to support Fixopost containing latanoprost 0.005% and timolol maleate 0.5% in single dose units and has been previously assessed.

In summary, Study LT2347-PIII-12/13 was a phase III, multicentre, randomised, investigator-masked, parallel-group, non-inferiority study conducted in 242 patients with open angle glaucoma (OAH) or ocular hypertension (OHT). All patients had a medical history of IOP insufficiently controlled with 1st line therapy (based on investigators' judgement) and at baseline all patients were stabilised on latanoprost+timolol with IOP ≤18 mmHg.

This study demonstrated that evening administrations of Fixopost were non-inferior to evening administrations of Xalacom, based on the upper limit of the 95% confidence interval for the difference (Fixopost minus Xalacom) not exceeding 1.5 mmHg.

The IOP mean change from baseline after 3 months of treatment was -0.49±1.8 mmHg in the Fixopost group and -0.49±2.25 mmHg in the Xalacom group with baseline IOP of 15.6±2.1 mmHg and 15.7±2.1 mmHg in the respective groups. As the IOP of the included patients were already controlled by latanoprost+timolol treatment, no pressure reducing effect was shown.

However, there were design and methodological concerns questioning if the performed study was sensitive enough to detect potential differences in effect between Fixopost and the reference product considering the differences in formulation between the two products with respect to preservative and other excipients. An assessment of the actual effect on elevated IOP was not feasible since all patients were stabilised on latanoprost+timolol at study entry.

Although acknowledging that there was no change in the current formulation compared to that of Monoprost, it is known that for latanoprost, the formulation is critical. However, it was not known whether this formulation had an impact on the efficacy of timolol, or whether the addition of timolol to the formulation had an impact on the characteristics of latanoprost and thereby its efficacy. Thus, a question was raised regarding the sensitivity of the study to show a difference in effect between the products.

In order to address the concerns raised and to support that the study population was sufficiently sensitive to detect differences, the Applicant submitted additional data including medical records from the study population, literature references of studies with cross-over design and studies showing the impact of preservatives.

The medical records, which were included in the response, included the last monotherapy received documented for 208 patients (86.0%), and IOP data could be analysed on a total of 176 patients (72.7%) in the ITT set (IOP data were not returned, missing or reported as "unknown" for 66 patients). Insufficiently controlled IOP was achieved with monotherapy. Based on the patients' medical records, the IOP was reduced following FDC treatment with Xalacom or generic latanoprost+timolol to 15.8±2.5 [95% CI: 15.3; 16.2] and 15.5±2.4 [95% CI: 15.1; 16.0], in the T2347 and Xalacom group,

respectively. The mean IOP change was -5.4±3.0 (25.6%) [95% CI: -6.0; -4.8] and -4.8±3.2 (23.5%) [95% CI: -5.5; -4.1] in the respective group.

The provided medical records showed an IOP decrease following latanoprost+timolol treatment in the total population (later randomised to Fixopost and Xalacom in the study), thus supporting that the patient population was sensitive and consequently in line with the proposed indication, 'insufficiently responsive to topical beta-blockers or prostaglandin analogues'.

The sensitivity of the population was further supported by literature of cross over studies in glaucoma patients treated with prostaglandin analogues and β-blockers. Patients treated with latanoprost/timolol fixed combination (LTFC) or the concomitant use of latanoprost + timolol were switched to timolol monotherapy which lead to IOP increase after 2-6 weeks. All the studies consistently showed that the IOP level was increased after patients were switched to a less effective treatment.

In addition, the Applicant presented a number of clinical trials comparing the efficacy of preserved *vs* unpreserved glaucoma therapies, including several prostaglandin analogues and timolol. Although there was no data on this specific formulation, the presented clinical trials comparing preserved vs unpreserved formulations showing no impact on efficacy, together with the demonstration of absence of impact of the excipients on the effect of latanoprost during the development of Monoprost, which alleviated the concern raised.

The results at Day 42 confirmed the primary analysis. In the mITT set, using the MMRM, the adjusted mean difference on Day 42 between the IOP change from baseline in the Fixopost group minus the IOP change from baseline in the Xalacom group was -0.19 [95% CI: -0.69; 0.31] for the worse eye. Similar results were shown for the contralateral eye.

In the mITT set, the proportion of patients with IOP < 18 mmHg in the worse eye and contralateral eye was consistent over time (i.e., at baseline [Day 0] before switching to Fixopost or Xalacom, and at Days 42 and 84 after the switch) in both treatment groups, and similar between the Fixopost and Xalacom groups at all assessment times (≥ 80%).

However, the single diurnal time point measurement to verify that the IOP lowering effect is appropriately maintained up to 24 hours was not considered sufficient. IOP was only measured once daily at 9 am and thus a consistent diurnal effect was not shown.

Also, collection of the efficacy variable, IOP change from baseline to Day 84 (primary end point) and to Day 42 (secondary end point) was not regarded as optimal to demonstrate a consistency throughout the 3-month period.

In the response submitted by the Applicant, the insufficient daily morning assessment of IOP was justified by numerous clinical studies including that of Monoprost and a preclinical study of Fixopost showing a 24-hour maintained IOP reduction.

Although it would have been preferred with a study design with anticipated peak and through effects, considering the well-established use of latanoprost+timolol with recognised effect, the single morning assessment was considered acceptable.

Although it would have been preferred to have additional assessments during the 3-month period, the arguments that the active substances tested are well-known, marketed and their long-term efficacy and safety well-established for decades were agreed.

In conclusion, although there were some limitations in the study design, considering the totality of data, including medical records and literature, it was considered sufficiently robust to resolve these issues.

IV.5 Clinical safety

No major safety differences were found between Fixopost and Xalacom. Eye disorders were somewhat more frequently reported in patients treated with Fixopost compared to Xalacom (11.8% vs 8.7% respectively). The most frequently reported ocular TEAE in either group was eye irritation (1.6% in the Fixopost group vs 4.3% in the Xalacom group). The most frequently reported TEAE in the Fixopost group was conjunctival hyperaemia (2.4%) vs 0.9% in the Xalacom group.

Overall, no new ocular ADRs were identified on Fixopost, that have not been well documented with the BAK-preserved latanoprost/timolol reference product.

The results of LT2347-PIII-12/13 indicated a better local tolerability of Fixopost compared to Xalacom, with less subjective symptoms throughout the day and upon instillation (in particular irritation/burning/stinging and itching). However, these symptoms were not reported as adverse events but as evaluation criteria, which was not considered adequate.

Regarding systemic ADRs, a few adverse events reported in the Fixopost group (dysguesia, arrhythmia, fatigue) had not been observed in clinical trials with the reference product; however, they are known for timolol, and already mentioned in Section 4.8 of Xalacom SmPC as additional AEs that have been reported specific to the use of this individual component of Xalacom.

The Applicant thus stated in Section 5.1 of FIXOPOST SmPC (Pharmacodynamic properties – Clinical efficacy and safety) as follows:
"A few systemic adverse reactions not seen in clinical trials with combined latanoprost/timolol preserved reference product (see section 4.8) have been observed in the two arms of the study: dysgeusia, arrhythmia, fatigue already well known for timolol were observed at a frequency uncommon", which was agreed.

However, Fixopost contains other excipients which could have an impact on safety. A pharmacovigilance action which included a targeted follow up questionnaire was implemented to monitor for long term ocular safety effects given the high concentration of macrogolglycerol hydroxystearate.

IV.6 Risk Management Plans

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Fixopost.

Safety specification
In the Day 160 response, the Applicant submitted RMP version 5.0 (signed 13 Oct 2020), in which the safety specification was aligned with the reference product as requested.

In addition, 'long-term ocular safety' (due to the high concentration of macrogolglycerol hydroxystearate) was included in the missing information section of the safety specification for Fixopost.

Summary of safety concerns	
Important identified risks	• Conjunctival hyperaemia • Eyelash and vellus hair changes • Periorbital skin discoloration • Iris hyperpigmentation • Herpetic keratitis • Cystoid macular oedema • Aggravation of asthma • Bronchospasm • Bradycardia
Important potential risks	None
Missing information	• Use in paediatric patients • Drug interactions • Use in pregnant and lactating women • Long-term ocular safety (due to the high concentration of macrogolglycerol hydroxystearate)

Pharmacovigilance Plan

Overall routine pharmacovigilance activities are considered sufficient to characterise and monitor most of the risks identified. In addition, the following pharmacovigilance action regarding the long-term ocular safety effects due to the high concentration of macrogolglycerol hydroxystearate is implemented for Fixopost:

Long-term ocular safety (due to the high concentration of macrogolglycerol hydroxystearate)		
Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
1 – None	Routine Targeted Follow-Up Questionnaire	The aim of this TFuQ is to obtain accurate information on the reported ocular reactions, which occurred more than 3 months after treatment initiation and to allow the assessment of the causal role of latanoprost or Cremophor RH 40, respectively. This targeted Follow up Questionnaire is presented in Appendix VII

Risk minimisation measures

Routine risk minimisation is considered sufficient, no additional risk minimisation activities are needed.

Summary of the RMP
The revised submitted Risk Management Plan, version 5.0, signed 13 October 2020 has been appropriately aligned with that of the reference product except for long-term ocular safety which has been added as additional missing information.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

IV.7 Discussion on the clinical aspects

Fixopost is the first preservative-free formulation FDC of latanoprost+timolol with the same concentration of active compounds as the reference product Xalacom, however, the excipients are considerably different. The benefits of preservative-free formulations are acknowledged. Generally, the safety profile of Fixopost is in line with the known profile of the latanprost+timolol combination with no new ocular ADRs identified, that have not been well documented with the BAK-preserved latanoprost/timolol reference product, Xalacom.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Fixopost SE/H/1602/01/DC and Monoprost FR/H/0499/002/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The efficacy of latanoprost+timolol combination and its place in the treatment of glaucoma and OHT have been well established. Xalacom is the reference formulation of latanoprost plus timolol in Europe. It contains a relatively high concentration (0.02%) of the preservative BAK.

The benefits of preservative-free formulations are acknowledged and particularly relevant for glaucoma patients at an advanced stage of the pathology, as they often present with ocular surface diseases, and generally require long-term treatment with more than one active agent.

One study was submitted for this hybrid application of a preservative free single dose fixed dose combination of latanoprost +timolol, Fixopost to establish a bridge to the reference product Xalacom, thereby allowing for a conclusion about therapeutic similarity.

Fixopost is a preservative-free formulation FDC of latanoprost+timolol with the same concentration of active compounds as the reference product Xalacom, however, the excipients are considerably different.

The same preservative free formulation of Fixopost is registered as a monocomponent, latanoprost, Monoprost, with reference product Xalatan.

Generally, the safety profile of Fixopost is in line with the known profile of the latanoprost+timolol combination with no new ocular ADRs identified, that have not been well documented with the BAK-preserved latanoprost/timolol reference product, Xalacom. Eye disorders were somewhat more frequently reported in patients treated with Fixopost compared to Xalacom (11.8% vs 8.7% respectively). The most frequently reported ocular TEAE in either group was eye irritation (1.6% in the Fixopost group vs 4.3% in the Xalacom group).

Since Fixopost is a hybrid of Xalacom, it was only studied on a limited period of 3-month, therefore few data are available concerning its long-term use. In order to monitor the long-term effect of the different excipients of Fixopost (castor oil), the MAH has proposed to add this safety concern in the RMP as missing information which has been accepted in the RMP. The safety specification of Fixopost has otherwise been appropriately aligned with the reference product.

To conclude the benefit risk of Fixopost is positive.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Fixopost, 50 micrograms/ml + 5 mg/ml eye drops, solution was positively finalised on 2020-11-18.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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