LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Fixopost
(latanoprost, timolol maleate)

SE/H/1602/001/DC

This module reflects the scientific discussion for the approval of Fixopost. The procedure was finalised on 2018-04-26. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Laboratoires THEA, has applied for a marketing authorisation for Fixopost, 50 µg/mL + 5 mg/mL eye drops, solution in single-dose container. The active substances are latanoprost and timolol. 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.

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 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 with T2347 eye drops to compare the efficacy, the pharmacokinetic profile and the local ocular tolerance of the proposed medicinal product and the reference product Xalacom®.

In addition, a non-clinical review of published relevant literature on the pharmacology, pharmacokinetics and toxicology of the active substances have been provided.

III.2 Pharmacology

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 and the efficacy 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.

One study was performed by the applicant to evaluate the ability of the T2347 ophthalmic formulation of latanoprost and timolol to reduce IOP in normotensive African green monkeys following topical delivery, in comparison with the reference product Xalacom® (Latanoprost 0.005% / Timolol 0.5%). Repeated topical administration of T2347 formulation resulted in a significant decrease of IOP in normotensive African green monkeys after 4 days of once daily treatment and remained significantly lower than baseline until the 92 hour time point, equivalent to 20 hours after the final dose of a 4-day once-daily dosing regimen. The IOP lowering effect of T2347 remained evident at the final time point at 96 hours (24 hours after

the final dose) but this effect was no longer significantly lower than measures at baseline. The reference product Xalacom elicited similar IOP lowering effects with significant IOP lowering effect observed at 84 hours after the initial dose. The duration of IOP lowering after a 4-day once-daily doses was shorter in response to Xalacom than observed following administration of T2347. The average maximal IOP lowering response to T2347 (6.0 mmHg) was marginally greater than that induced by Xalacom (5.6 mmHg) but this difference was not statistically significant. The similarity in IOP changes induced with both treatments reflects the use of identical active agents, latanoprost and timolol. No adverse systemic or ocular events were reported following topical administration. Based on the well-known effect of latanoprost and timolol on the IOP in man, the study in monkeys seems redundant and may have been omitted from a 3R perspective.

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 pharmacokinetical 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 instillation for 14 days in both eyes of pigmented rabbits of the T2347 formulation and the reference product Xalacom®. Following one daily instillation for 14 days in both eyes of T2347 or Xalacom, the concentration of timolol in plasma increased up to 1h and decreased thereafter. No timolol was found in plasma at the residual time (24 h after the 13^{th} 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 animal 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 was performed in albino rabbits to compare the ocular tolerance of unpreserved T2347 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 test formulation T2347 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 coefficient log Pow, determined by the applicant, are respectively 4.2 for latanoprost and -0.6 for timolol. As the log Kow 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, and a review of published relevant literature (clinical pharmacology, clinical efficacy and clinical safety).

Type of study	Efficacy and safety Phase III
Study ID	LT2347-PIII-12/13
Objectives	To assess efficacy and safety of T2347 (FIXOPOST) versus Xalacom in patients with OAG or OHT.
Study design and type of control	Phase III, international, multicentre, randomised, parallel group, investigator-masked study Comparison versus reference product
Test product; **Dosage Regimen;** **Route of administration**	FIXOPOST (T2347) (unpreserved latanoprost 0.005% plus timolol 0.5% eye drops in SDU) Versus Xalacom (BAK-preserved latanoprost 0.005% plus timolol 0.5% eye drops in MD bottles)
No. of subjects (mITT set)	FIXOPOST: 124 Xalacom: 112 Total: 236
Diagnosis of patients	Open angle glaucoma (OAG) or ocular hypertension (OHT) in both eyes, already treated and controlled by Xalacom or generics (fixed combination latanoprost 50 µg/mL + timolol 5 mg/mL preserved eye drops) for at least 2 months; IOP ≤ 18 mmHg in both eyes; history of IOP insufficiently controlled with first-line monotherapy based on the investigator's judgement (*e.g.*, not reaching the target IOP); history of an add-on IOP reduction with Xalacom or generics (fixed combination latanoprost 50 µg/mL + timolol 5 mg/mL preserved eye drops) in comparison with first-line treatment; corneal thickness ≥ 500 µm and ≤ 600 µm in both eyes.
Duration of treatment	3 months (from Day 0 to Day 84)

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 (Cmax 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 are provided. Pharmacodynamics is appropriately described in the SmPC.

IV.4 Clinical efficacy

The Applicant provides an appropriate review of published literature. 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 new preservative free FDC of latanoprost+timolol and the same formulation is already approved in a mono-composition of latanoprost (Monoprost).

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.

Study LT2347-PIII-12/13, was a phase III, multicentre, randomised, investigator-masked, parallel-group, non-inferiority study conducted in 242 patients with OAH or 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 Clinical Phase III study demonstrate 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.

However, there were design and methodological concerns questioning if the performed study is 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. These issues were addressed by the Applicant in the D106 response document.

Although acknowledging that there is no change in the current formulation compared to that of Monoprost, it is known that for latanoprost, the formulation is critical. However, it is not known whether this formulation has an impact on the efficacy of timolol, or whether the addition of timolol to the formulation has an impact on the characteristics of latanoprost and thereby its efficacy.

The IOP of the included patients were already controlled by latanoprost+timolol treatment, and thus no pressure reducing effect was shown. 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. An assessment of the actual effect on elevated IOP is thus not feasible since all patients were stabilised on latanoprost+timolol at study entry. 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 present study population is 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 respective group.

The provided medical records show 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 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 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 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, alleviates 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%).

In addition, the single diurnal time point measurement to verify that the IOP lowering effect is appropriately maintained up to 24 hour is not 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) is not regarded as optimal to demonstrate a consistency throughout the 3 months period.

In the response submitted from the Applicant, the insufficient daily morning assessment of IOP is 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 is considered acceptable.

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

To summarise:

- The tested product is a hybrid application and the active ingredients are well characterised
- The sensitivity of the population was supported by medical records showing a consistent IOP lowering effect of latanoprost+timolol, after switch from monotherapy
- The anticipated sensitivity of the population was further supported by the data from cross over studies
- The absence of impact of the preservative on the IOP-lowering effect was supported by literature together with data from the Monoprost development

In conclusion, although there are some limitations in the study design, considering the totality of data, including medical records and literature, it is considered sufficiently robust to resolve this issue.

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 (Treatment emergent adverse event) 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 was conjunctival hyperaemia, 2.4% vs 0.9% in the Xalacom group.

Analysis of ADRs reported shows that no new ocular ADRs were identified on FIXOPOST that have not been well documented with the BAK-preserved latanoprost/timolol reference product.

Safety results of Study 12/13 conducted by the Applicant 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 is not 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 proposal to update 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”, is agreed.

FIXOPOST contains other excipients such as macrogolglycerol hydroxystearate (castor oil polyoxyl hydrogenated), sorbitol, carbomer and macrogol which could have an impact on the safety of FIXOPOST. In particular, macrogolglycerol hydroxystearate is known to induce skin reactions. The pharmacovigilance action proposed regarding the long term ocular safety effects

due to the high concentration of macroglycerol hydroxystearate, is endorsed, including a targeted follow up questionnaire (See RMP below).

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 Concerns

Summary of safety concerns in RMP v. 2.1, with DLP of 30 April 2017 submitted by the Applicant.

Summary of safety concerns	
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	• Paediatrics patients • Drug interactions • Pregnant and lactating women • Long-term ocular safety (due to the high concentration of macrogolglycerol hydroxystearate)

Pharmacovigilance Plan

Routine pharmacovigilance is suggested by the applicant..
For the missing information of long term ocular safety,the following routine pharmacovigilance activity is planned for FIXOPOST.

Long-term ocular safety (due to 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 ignition and to allow the assessment of the causal role of latanoprost or Cremaphor RH 40, respectively.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The RMP, version 2.1 is approvable.

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.
The MAH has satisfactory responded to the questions raised and updated the RMP accordingly.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

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+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 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. FIXOPOST is a preservative-free solution packaged in single dose containers, contrary to Xalacom which contains a preservative (BAK) and is a multidose product.

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 months, 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.

To conclude, the benefit risk of FIXOPOST, 50 µg/mL + 5 mg/mL eye drops is positive.

There are no objections to approval of FIXOPOST, 50 µg/mL + 5 mg/mL eye drops, from a clinical point of view.

The product information is acceptable.

FIXOPOST, 50 µg/mL + 5 mg/mL eye drops is acceptable from a Quality point of view.

FIXOPOST, 50 µg/mL + 5 mg/mL eye drops is acceptable from a Non-clinical point of view.

The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 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

Decentralised procedure for FIXOPOST, 50 µg/mL + 5 mg/mL eye drops, solution in single-dose container was positively finalised on 2018-04-26.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	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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