



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Tafluprost / Timolol

Proprietary Product Name: Taptiqom 15/5

Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd

July 2015

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- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
ADR	adverse drug reaction
AE	adverse event
CHMP	Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
ICH	International Conference on Harmonization
IOP	Intraocular pressure
N/A	Not Applicable
PIL	Patient information leaflet
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SAE	Serious Adverse Experience
SDU	Single dose unit
SmPC	Summary of Product Characteristics (EU)
TT-FDC	Taptiqom

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New Fixed Dose Combination
<i>Decision:</i>	Approved
<i>Date of decision:</i>	29 January 2015
<i>Active ingredient(s):</i>	Tafluprost / Timolol
<i>Product name(s):</i>	Taptiqom 15/5
<i>Sponsor's name and address:</i>	Merck Sharp & Dohme (Australia) Pty Ltd Locked Bag 334 North Ryde NSW 1670
<i>Dose form(s):</i>	Eye Drop Solution
<i>Strength(s):</i>	Tafluprost 15 micrograms/mL and Timolol (as maleate) 5 mg/mL
<i>Container(s):</i>	Single use ampoules
<i>Pack size(s):</i>	30 x 0.3 mL (and 10 x 0.3 mL starter pack)
<i>Approved therapeutic use:</i>	<i>Taptiqom 15/5 is indicated for the reduction of intraocular pressure (IOP) in adult patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to beta blockers or prostaglandin analogues and require a combination therapy.</i>
<i>Route(s) of administration:</i>	Topical (ocular)
<i>Dosage:</i>	Adults: Recommended therapy is one eye drop in the conjunctival sac of the affected eye(s) once daily. Taptiqom 15/5 is not recommended for use in children and adolescents below the age of 18 years.
<i>ARTG number (s):</i>	218042

Product background

This AusPAR describes the application by Merck Sharp & Dohme (Australia) Pty Limited (MSD) to register Taptiqom¹, a new fixed-dose combination of tafluprost and timolol. Taptiqom is to be used to reduce intraocular pressure in adults with open angle glaucoma or ocular hypertension. The sponsor proposed the following indications:

¹ The sponsor formally requested in their pre-ACPM response dated 14 November 2014 that the proposed trade name Taptiqom be changed to Taptiqom 15/5 to reflect the strengths of the two active ingredients in the product.

Taptiqom is indicated for the reduction of intraocular pressure (IOP) in adult patients with open angle glaucoma or ocular hypertension when concomitant therapy is appropriate.

Medical therapy of open angle glaucoma or ocular hypertension is usually used before laser or surgery, although there is some evidence to show that initial laser treatment is as efficacious and safe as initial medical treatment.

If medical therapy is chosen as the initial therapy, then prostaglandins are usually regarded as first-line treatment because they are considered more effective than beta-blockers, carbonic anhydrase inhibitors or alpha adrenergic agonists. Prostaglandins are also considered to have a better adverse-event profile than the alternatives. Adding a second agent from a different class is a reasonable strategy if initial monotherapy is not effective.

Tafluprost is a fluorinated analogue of prostaglandin F2alpha. Tafluprost acid, the biologically active metabolite of tafluprost, is a highly potent and selective agonist of the human prostanoid FP receptor, which is thought to reduce intra-ocular pressure (IOP) by increasing uveoscleral outflow of aqueous humour. Tafluprost acid has a 12 fold higher affinity for the FP receptor than latanoprost.

Timolol is a non-selective beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant or local anaesthetic (membrane-stabilising) activity. It combines reversibly with a part of the cell membrane, the beta-adrenergic receptor, and inhibits the usual biologic response that would occur with stimulation of that receptor; that is, it reduces intra-ocular pressure by reducing aqueous formation.

A single container with a Fixed Dose Combination (FDC) of tafluprost and timolol has two putative advantages:

- Reducing the wash-out effect of administering multiple drops to the eye.
- Increasing patient compliance.

The submission proposes registration of the following dosage form and strength:

- Tafluprost 15 micrograms/mL and timolol (as maleate) 5 mg/mL Fixed Dose Combination in a single dose eye drop ampoule.

Other similar combinations of a prostaglandin and a beta-blocker are already registered on the Austrian Register of Therapeutic Goods (ARTG):

- Xalacom (latanoprost + timolol)
- Latanocom (latanoprost + timolol)
- Duotrav (travoprost + timolol)
- Ganfort (bimatoprost + timolol)

For more details of these products see *Regulatory status* below.

Regulatory status

This is an application for a new fixed dose combination of registered drugs.

At the time the TGA considered this application, a similar application had been approved in the European Union (EU) on 17 June 2013 (see Table 1 below).

Table 1: International regulatory status

Country/Region	Date submitted	Date approved	Indication
European Union Decentralised Procedure Reference Member State: Germany	17 June 2013	End of procedure advised on 02 October 2014 as approvable	Reduction of intraocular pressure (IOP) in adult patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to topical monotherapy with beta-blockers or prostaglandin analogues and require a combination therapy, and who would benefit from preservative free eye drops.

Monotherapy eye drops containing a solution of tafluprost at 15 mg/mL received initial registration on the ARTG as Saflutan (AUST R 168803) by MSD and timolol maleate (Tenopt AUST R 19795; Aspen Pharma Pty Ltd) has been on the ARTG since 1996.

Saflutan has a similar indication to that proposed for Taptiqom:

For the reduction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension, as monotherapy or as adjunctive therapy to beta blockers.

MSD also markets eye drops containing a solution timolol (as maleate) at 5 mg/mL under the trade name Timoptol (AUST R 28775) with the indication:

For the reduction of elevated intraocular pressure. In clinical trials it has been shown to reduce intraocular pressure in: Patients with ocular hypertension - Patients with chronic open-angle glaucoma - Aphakic patients with glaucoma'.

Xalacom is registered for:

- *Reduction of elevated intraocular pressure in patients with open-angle glaucoma and ocular hypertension who are insufficiently responsive to beta-blockers, prostaglandins or other intraocular pressure lowering medications. Xalacom should not be used to initiate therapy.*
- *Reduction of elevated intraocular pressure in patients with open-angle glaucoma and ocular hypertension who are insufficiently responsive to beta-blockers, prostaglandins or other intraocular pressure lowering medications. Latanocom should not be used to initiate therapy.*

• Duotrav is registered for:

- *Reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension for whom single agent therapy provides insufficient intraocular pressure reduction.*

• Ganfort PF is registered for the following indications:

- *Indicated for the reduction of intraocular pressure (IOP) in patients with chronic open-angle glaucoma or ocular hypertension who are insufficiently responsive to monotherapy.*

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Quality findings

Introduction

According to the draft PI, the maximum daily dose is 1 drop per eye each day. Therefore given the drop size of 31 μL , the maximum daily dose of tafluprost is 0.93 $\mu\text{g}/\text{day}$ and the maximum daily dose of timolol is 310 $\mu\text{g}/\text{day}$.

Drug substance (active ingredient)

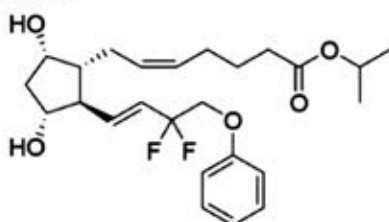
All details relating to the manufacture, control and storage of the tafluprost are as for the currently registered monotherapy Saflutan eye drops.

The details of the timolol maleate are new to this submission. The material is controlled to the British Pharmacopoeia (BP)/European Pharmacopoeia (EP) monograph for timolol maleate with additional tests for residual solvents and microbial quality. This is adequate for this product.

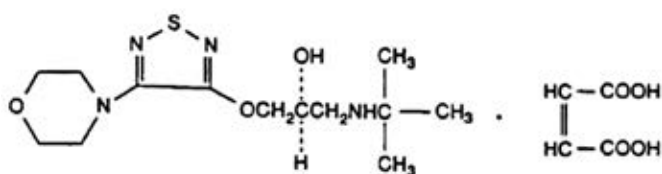
The chemical structure of Tafluprost and timolol are shown in Figure 1 below.

Figure 1: Chemical structure of active ingredients

Tafluprost



Timolol maleate



Drug product

The product contains no unusual excipients for this dosage form. The base solution (which is closely related to the base solution of the monotherapy Saflutan eye drops) contains polysorbate 80 as a solubilising agent, disodium edetate as a chelator, disodium phosphate as a buffering agent, water as the solvent and glycerol to make it isotonic. During manufacture the pH is adjusted to 6.2 to 6.6 and it is unpreserved.

Manufacture is typical for an eye drop solution but involves no terminal sterilisation step. Thus, the drug substance solution is sterilised by filtration and filled into the low density polyethylene (LDPE) ampoules using a blow-fill-seal operation. This operation means that the ampoules are also sterile.

The Microbiology Section at the TGA has stated that the microbiological and sterility aspects are acceptable.

The manufacture gives 10 ampoules linked together and these are packed into an aluminium laminated pouch. The starter pack includes one pouch and the commercial pack 3 pouches.

There are no compendial monographs for the product but the specifications for the product ensure the BP/EP general requirements for eye drops are met. The chemistry and physical tests and limits within the specifications and where required the release limits are tighter than the expiry limits to allow for changes on storage.

The specifications also include a test and limits for sterility that was acceptable to the Microbiology Section at TGA.

In relation to the shelf life, data was included to support an unopened shelf life of 3 years when stored at 2 to 8°C (refrigerate do not freeze) and an in-use shelf life of 4 weeks (28 days) when stored below 25°C and returned into the laminate pouch.

The PI and labels have been finalised with respect to chemistry and quality control.

Biopharmaceutics

This product is for ocular use and is intended to act without systemic absorption. As a consequence no bioavailability data were required to be submitted (and none were provided). However it must be noted that the individual components of this fixed dose combination product may be differently absorbed into the eye and systemically compared to when given as monotherapies.

Advisory committee considerations

Given that there were no issues with the chemistry, manufacturing and control aspects of the submission and there were no bioavailability data, details relating to this submission were not presented to Pharmaceutical Subcommittee (PSC).

Quality summary and conclusions

Approval of the registration of the proposed product can be recommended in relation to chemistry, manufacturing and control.

III. Nonclinical findings

Introduction

The nonclinical submission contained studies on pharmacokinetics and repeat-dose toxicity. The scope of the nonclinical program is in accordance with the TGA adopted EU guideline *Guideline on the Nonclinical Development of Fixed Combinations of Medicinal Products (EMA/CHMP/SWP/258498/2005)*.

Pharmacology

No nonclinical pharmacodynamic studies with the combination were submitted. This combination of pharmacological classes (a prostaglandin F2-alpha analogue and a beta-adrenoceptor antagonist) for the proposed indication is not novel.

Pharmacokinetics

Corneal penetration of tafluprost was seen to be comparable or slightly lower ($\leq 9\%$), and that of timolol also slightly lower (approximately 20%), with topical ocular administration of the combination formulation in rabbits compared to that of administration of either agent singly. Systemic exposure data in monkeys showed no obvious or consistent pharmacokinetic interaction. Similar or slightly lower systemic exposure in humans with the combination compared to either agent as monotherapy is indicated by data reported in the sponsor's Clinical Overview.

Toxicology

A Good Laboratory Practice (GLP) compliant, 3 month repeat-dose toxicity study was conducted with a combination of tafluprost and timolol in Cynomolgus monkeys. The duration of the study and the use of a single species are consistent with the relevant TGA adopted EU guideline.² Administration was by the clinical route (topical ocular; 30 μ L), twice daily (compared to once daily dosing in patients) to one eye only at either the proposed clinical strength of the active ingredients (0.0015%/0.5% tafluprost/timolol) or at a strength 3 times higher than the clinical strength. Parallel single agent groups were included in the study. Full formulation details were not provided but the limited information presented supports that the proposed clinical formulation was not used (that is, test items contained the preservative benzalkonium chloride). Routine histopathological examination was limited to ocular tissues only. This is considered to be acceptable given the lack of obvious systemic toxicity in the study plus previous nonclinical studies with the single agents that raise no particular concerns.

Plasma area under the plasma concentration versus time curve (AUC) values for tafluprost acid (active metabolite) and timolol in monkeys at the high-dose level were approximately 12 to 60-times higher than anticipated in patients.

Notable findings in monkeys were limited to darkening of treated eyes (attributable to tafluprost) and a suggestion of a reduction in intraocular pressure with the two drugs alone or in combination- the expected pharmacological effect. The lack of a clear effect on intraocular pressure may reflect that the animals were ocular normotensive.

One of the pharmacokinetic studies in rabbits conducted with the clinical formulation included gross examination of ocular tolerance. Transient mild conjunctival redness was seen with the combination, occurring more frequently than the single-agent timolol but less frequently than the single-agent tafluprost.

Pregnancy classification

The sponsor has proposed Pregnancy Category C³. This is appropriate based on the existing categories for single agent tafluprost and timolol products (B3⁴ and C, respectively).

² Guideline of the Nonclinical Development of Fixed Combinations of Medicinal Products (EMA/CHMP/SWP/258498/2005)

³ Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

⁴ Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Nonclinical summary and conclusions

- The strengths and resultant doses of the two active ingredients in Taptiqom are in line with that approved for related single agent products.
- The nonclinical submission contained studies on pharmacokinetics and repeat-dose toxicity. There were no major deficiencies in the data package.
- No nonclinical efficacy study with the combination was submitted.
- The ocular absorption of tafluprost and timolol was comparable or slightly lower with co-administration compared to that of dosing with each agent alone in rabbits. No systemic pharmacokinetic interaction was evident in monkeys.
- No novel or exacerbated toxicity was observed with the combination compared to that of the single agents in a 3 month study in monkeys involving twice daily dosing with eye drops containing the drugs at the proposed clinical strength or 3 times higher than the proposed clinical strength. Acceptable ocular tolerance was shown in a study in rabbits conducted with the commercial formulation.
- There are no nonclinical objections to the registration of Taptiqom for the proposed indications. Revisions to the draft PI were recommended but these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical Rationale

The sponsor states the rationale for the new fixed dose combination product to be:

Options for the treatment of glaucoma include: a non-selective beta-adrenoceptor blocking agent such as timolol, carbonic anhydrase inhibitor such as dorzolamide and prostaglandin analogues such as tafluprost, latanoprost, travaprost and bimatoprost as individual agents. Where the IOP reduction by a single agent has not been considered clinically adequate, combinations have been used since the individual products act via different mechanisms of action to illicit the IOP lowering effect. It is generally believed that prostaglandins reduce IOP by increasing uveoscleral outflow of aqueous humour and timolol reduces the aqueous formation. The combination of a beta-adrenoceptor blocking agent and a prostaglandin as proposed in this new combination is not uncommon. At present there are already similar combinations that are registered on the ARTG: latanoprost + timolol as Xalacom (AUST R 80311) and Latanocom (AUST R 183346); travoprost + timolol as Duotrav (AUST R 125607, 177772); and bimatoprost + timolol as Ganfort (AUST R 147830). The concentrations used in the combination products are generally the same as those used in the individual mono-component products.

A single container with a fixed combination of tafluprost and timolol has multiple advantages. First, the well-known 'washout' effect resulting in decreased efficacy of the combination will be reduced; this occurs when a second topical drop is administered to the eye within five minutes of the first administered drop causing a washout loss of the latter. Second, by reducing the number of daily drops administered from three to one, patient compliance is expected to improve due to a

simplified drug regimen. Reducing the number of daily drops a glaucoma patient must administer may improve compliance. Poor compliance with topical medications in glaucoma patients is associated with elevated IOP and progressive disease.

Contents of the clinical dossier

Scope of the clinical dossier

The submission contained the following clinical information:

- One clinical pharmacology study that provided pharmacokinetic data.
- Two pivotal efficacy/safety studies.
- Four other efficacy/safety studies using a related product in a Japanese population (DE-111).

Paediatric data

The submission did not include paediatric data. The sponsor has been granted a waiver for a Paediatric Investigation Plan: EMEA-002116-PIP01-12. The waiver covers all subsets of the paediatric population from birth to <18 years of age. The waiver was granted '*on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments*'.

Good clinical practice

The clinical data presented in the submission were stated to have been, and appeared to have been, obtained using Good Clinical Practice (GCP).

Pharmacokinetics

Studies providing pharmacokinetic data

Table 2 shows the studies relating to each pharmacokinetic topic.

Table 2: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK interactions	Tafluprost and Timolol	Study 201150
	Tafluprost and Timolol	Study 01111002

Neither of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

Both tafluprost and timolol have low systemic bioavailability when administered by the ocular route. Neither compound influenced the PK of the other.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 3 shows the studies relating to each pharmacodynamic topic.

Table 2. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on IOP	Study 201150

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

Tafluprost and timolol in combination have an additive pharmacodynamic effect.

Dosage selection for the pivotal studies

The doses used in the pivotal studies were selected on the basis of the approved dosing for tafluprost and timolol as individual treatments.

Efficacy

Studies providing efficacy data

Two pivotal efficacy/safety studies were submitted and evaluated. Four supportive studies were also included.

Evaluator's conclusions on efficacy for reduction of IOP

Taptiqom (tafluprost 15 micrograms/mL and timolol [as maleate] 5 mg/mL) was superior to either active component administered as monotherapy and non-inferior to both active components administered concomitantly. In comparison with timolol as monotherapy (TM) the mean difference (95% Confidence Interval (CI)), FDC - TM, in change from baseline in average diurnal IOP at 3 months was -0.885 (-1.745 to -0.044), $p = 0.044$. In comparison with tafluprost as monotherapy (TM) the mean difference (95% CI), FDC - TM, in change from baseline in average diurnal IOP at 3 months was -1.516 (-2.044 to -0.988), $p < 0.001$. In comparison with timolol and tafluprost administered concomitantly the treatment difference in IOP at Month 6 was 0.308 (-0.194 to 0.810) mmHg.

The secondary efficacy outcome measures supported the primary efficacy outcome measures. The data from a similar product (preservative containing FDC tafluprost 0.0015% and timolol 0.5%) were also supportive of the pivotal studies.

The criterion for non-inferiority was clinically significant and the statistical analysis was appropriate. The population included in the pivotal studies was similar to the patient population intended for marketing in Australia.

Safety

Studies providing safety data

There were no pivotal studies that assessed safety as a primary outcome.

Two pivotal studies, one PK study and four supportive studies provided evaluable safety data.

In the pivotal efficacy studies, the following safety data were collected:

- Adverse events (AEs)
- Ocular safety measures and local tolerability
- Laboratory tests
- Vital signs

Patient exposure

- In Study 201150, there were 14 healthy volunteers treated with FDC once daily for 8 days.
- In Study 01111002, 16 healthy Japanese male volunteers were exposed to DE-111 for one week.
- In Study 201050, there were 283 subjects treated for up to 6 months with FDC.
- In Study 201051, there were 201 subjects exposed to FDC for up to 6 months. There were 198 subjects treated in the left eye and 192 in the right eye.
- In Study 01111004, there were 161 subjects exposed to DE-111 for up to 4 weeks.
- In Study 01111005 (Module 5, Section 5.3.5.4), summarized in Table 1.2.3, there were 82 subjects treated with DE-111 for up to 4 weeks.
- In Study 01111006, there were 136 subjects exposed to DE-111 for up to 52 weeks, with 115 exposed for >180 days.

Postmarketing data

No postmarketing data were included in the submission.

Evaluator's conclusions on safety

The safety profile of the FDC combination product is similar to that for the individual products administered concomitantly. The adverse event profile for the FDC reflects that of the individual components. The safety data did not identify any new safety issue as a result of concomitant administration.

The majority of AEs were ophthalmic (ocular hyperaemia, eyelash lengthening, eyelid discolouration). There were few serious AEs (SAEs) and no deaths during the development program.

First round benefit-risk assessment

First round assessment of benefits

Taptiqom (tafluprost 15 micrograms/mL and timolol [as maleate] 5 mg/mL) was superior to either active component administered as monotherapy, and non-inferior to both active

components administered concomitantly. In comparison with timolol as monotherapy the mean difference (95% CI), FDC - TM, in change from baseline in average diurnal IOP at 3 months was -0.885 (-1.745 to -0.044), $p = 0.044$. In comparison with tafluprost as monotherapy the mean difference (95% CI), FDC - TM, in change from baseline in average diurnal IOP at 3 months was -1.516 (-2.044 to -0.988), $p < 0.001$. In comparison with timolol and tafluprost administered concomitantly the treatment difference in IOP at Month 6 was 0.308 (-0.194 to 0.810) mmHg.

The secondary efficacy outcome measures supported the primary efficacy outcome measures. The data from a similar product, preservative containing FDC tafluprost 0.0015% and timolol 0.5%, were also supportive of the pivotal studies.

The criterion for non-inferiority was clinically significant and the statistical analysis was appropriate. The population included in the pivotal studies was similar to the patient population intended for marketing in Australia.

First round assessment of risks

The safety profile of the FDC combination product is similar to that for the individual products administered concomitantly. The adverse event profile for the FDC reflects that of the individual components. The safety data did not identify any new safety issue as a result of concomitant administration.

The majority of AEs were ophthalmic (ocular hyperaemia, eyelash lengthening and eyelid discolouration). There were few SAEs and no deaths during the development program.

First round assessment of benefit-risk balance

The benefit-risk balance of Taptiqom (tafluprost 15 micrograms/mL and timolol [as maleate] 5 mg/mL), given the proposed usage, is favourable.

First round recommendation regarding authorisation

The clinical evaluator would have no objection to the approval of Taptiqom (tafluprost 15 micrograms/mL and timolol [as maleate] 5 mg/mL) for the indication of:

Taptiqom is indicated for the reduction of intraocular pressure (IOP) in adult patients with open angle glaucoma or ocular hypertension when concomitant therapy is appropriate.

Clinical questions

No questions were raised by the clinical evaluator.

Second round evaluation of clinical data submitted in response to questions

No second round evaluation was required.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted the EU Risk Management Plan (EU-RMP), Version 1 (dated 29 April 2013) with an undated Australian Specific Annex (ASA), which were reviewed by the TGA's Post-Market Surveillance Branch (PMSB).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 3.

Table 3: Summary of ongoing safety concerns

Summary of safety concerns	
Important identified risks	Hyperpigmentation, Reactive airway disease including bronchial asthma / a history of bronchial asthma, Severe chronic obstructive pulmonary disease, Sinus bradycardia, Sick sinus syndrome (including sino-atrial block), Second or third degree atrioventricular block not controlled with pace-maker, Overt cardiac failure, Cardiogenic shock.
Important potential risks	Vascular disorders, Masking of hypoglycemic symptoms in patients with diabetes mellitus, Masking of thyrotoxicosis, Surgical anesthesia, Choroidal detachment, Anaphylaxis
Important missing information	Children and adolescents have not been studied in clinical trials. Therefore, TT-FDC is not recommended for use in children or adolescents below age 18. Use in renal impairment. Use in hepatic impairment. Use in pregnancy and in breast-feeding women.

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities to monitor all the specified ongoing safety concerns.

Risk minimisation activities

The sponsor has concluded that routine risk minimisation activities for all the specified ongoing safety concerns are sufficient.

Reconciliation of issues outlined in the RMP report

Table 4 summarises the PMSB's first round evaluation of the RMP, the sponsor's responses to issues raised by the PMSB and the PMSB's evaluation of the sponsor's responses.

Table 4: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	PMSB evaluator's comment
<p>1. The pagination stated in the 'Table of Contents' of the ASA needs to be corrected when this document is next updated. It is also suggested that appropriate document control be applied to the ASA.</p>	<p>The sponsor states: <i>'No change has been made to the ASA initially submitted to the TGA, therefore the ASA Table of Content does not need to be updated.'</i></p>	<p>Unfortunately it appears the sponsor has not checked the pagination in the 'Table of Contents' of the ASA and not identified the observed inconsistencies. Consequently this issue remains outstanding and a corrected ASA, which should be appropriately version controlled and dated, must be provided to the TGA for review before this application is approved.</p>
<p>2. Safety considerations may be raised by the nonclinical and clinical evaluators through the TGA's consolidated request for further information and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is</p>	<p>The sponsor makes no specific response to this recommendation.</p>	<p>The nonclinical and clinical evaluators did not raise any additional safety considerations.</p>

Recommendation in RMP evaluation report	Sponsor's response	PMSB evaluator's comment
<p>relevant and necessary to address the issue in the RMP.</p>		
<p>3. In comparison to what was previously accepted for Saflutan, the following material differences are observed in the summary of the Ongoing Safety Concerns:</p> <p>The important potential risk: 'Embryotoxicity' has been deleted.</p> <p>The important potential risk: 'Possible drug interaction; combination of tafluprost and other prostaglandin analogues' has not been included as an ongoing safety concern.</p> <p>The important missing information: 'Patients with aphakia', 'Patients with neovascular, angle-closure, narrow angle, pseudoexfoliative or congenital glaucoma' & 'Patients wearing contact lenses' have not been included as ongoing safety</p>	<p>The sponsor concedes: <i>'Embryotoxicity has been seen in animal testing with tafluprost.'</i> However, then states: <i>'After reassessing the risks for tafluprost, embryotoxicity was not considered anymore as an important potential risk for humans'</i> without providing detail of any such reassessment or new evidence.</p> <p>The sponsor states that the important potential risk: 'Possible drug interaction; combination of tafluprost and other prostaglandin analogues' <i>'is mentioned as an important potential risk only in the tafluprost RMP and it is not in line with the tafluprost EU SmPC: 'No interactions are anticipated in humans, since systemic concentrations of tafluprost are extremely low following ocular dosing. Therefore, specific interaction studies with other medicinal products have not been performed with tafluprost.'</i></p> <p>The sponsor states: <i>'Tafluprost EU SmPC ('There is no experience with tafluprost in neovascular, angle-closure, narrow-angle</i></p>	<p>This response is considered inadequate. Consequently this issue remains outstanding (see 'Outstanding issues').</p> <p>This possible drug interaction is in the context of reports of paradoxical elevations in intraocular pressure. Consequently the sponsor's reassessment of this risk is considered inadequate and this issue remains outstanding (see 'Outstanding issues').</p> <p>In general this response is acceptable, except for the absence of any comment on the important missing information: 'Patients wearing contact lenses' and the sponsor's refusal to amend the ASA accordingly.</p>

Recommendation in RMP evaluation report	Sponsor's response	PMSB evaluator's comment
<p>concerns.</p> <p>No explanation appears to have been provided for these differences.</p> <p>Notwithstanding the evaluation of the nonclinical and clinical aspects of the SS, it is recommended that the sponsor should provide compelling justification for these deletions/omissions. Alternatively if the sponsor decides to include these ongoing safety concerns in Australia for Taptiqom, then consideration must be given as to what pharmacovigilance and risk minimisation activities will be proposed for them and the ASA should be revised accordingly.</p>	<p><i>or congenital glaucoma. There is only limited experience with tafluprost in aphakic patients and in pigmentary or pseudoexfoliative glaucoma') and RMP are in line with each other. The statement was mistakenly left out from Taptiqom RMP and will be considered as missing information. Taptiqom RMP will be corrected accordingly. Since the Australian PI is consistent with the EU SmPC, and this statement will be included in the EU RMP, the ASA will not be updated. We provide an assurance that an updated RMP will be provided to the TGA at the next opportunity.'</i></p>	<p>Consequently this issue remains outstanding until the important missing information: 'Patients with aphakia', 'Patients with neovascular, angle-closure, narrow angle, psuedoexfoliative or congenital glaucoma' & 'Patients wearing contact lenses' are included as ongoing safety concerns as reflected in a revised ASA and consideration given as to what pharmacovigilance and risk minimisation activities will be proposed for them.</p>
<p>4. At this time there are no objections to the pharmacovigilance activities proposed by the sponsor. Nevertheless the ASA may need to be revised if additional ongoing safety concerns are included.</p>	<p>The sponsor makes no specific response to this recommendation, but has declined to include any additional ongoing safety concerns.</p>	<p>As discussed above the refusal to include any additional ongoing safety concerns is considered inadequate. An adequately revised ASA should be submitted for review before this application is approved. In addition this table should be re-titled 'Summary of the Australian Risk Management Plan', as it refers to both pharmacovigilance and risk</p>

Recommendation in RMP evaluation report	Sponsor's response	PMSB evaluator's comment
		minimisation activities.
5. At this time the specified ongoing safety concerns would not appear to warrant additional risk minimisation activities, therefore the sponsor's conclusion that routine risk minimisation activities for all the specified ongoing safety concerns are sufficient is acceptable.	The sponsor makes no specific response to this recommendation.	Not applicable
6. At this time the sponsor's handling of the potential for medication errors using routine pharmacovigilance and risk minimisation activities is acceptable.	The sponsor makes no specific response to this recommendation.	Not applicable
7. At this time the sponsor's proposed application of routine risk minimisation activities would appear to be reasonable and therefore generally acceptable. Nevertheless, the ASA may need to be revised if additional ongoing safety concerns are included. Furthermore as per the <i>Risk Management Plan (RMP) Questions and Answers (Version 1.3,</i>	The sponsor states: <i>'The differences between the PI and the SmPC are minor and have no impact on the level of safety profile as described in the RMP and ASA. Therefore no change has been made to the ASA.'</i>	This is not entirely satisfactory. Consequently it is recommended that the ASA should include a risk minimisation activities table, which compares the actual content and wording of the current EU SmPC and the proposed Australian PI & CMI for all of the specified ongoing safety concerns and missing

Recommendation in RMP evaluation report	Sponsor's response	PMSB evaluator's comment
<p><i>October 2012)</i> as found on the TGA website, these guidelines state: <i>'The ASA should identify any differences between the EU-RMP and the local implementation of risk management activities, for example: any differences between the risk minimisation activities undertaken as reflected in the content of the EU Summary of Product Characteristics (SmPC) and the proposed Australian Product Information (PI), and the reasons for the difference. This will allow the TGA to assess the appropriateness of the proposed RMP in the Australian environment.'</i> Consequently the sponsor should identify and provide reasons for any differences between the risk minimisation activities undertaken as reflected in the content of the EU SmPC and the proposed Australian PI in a revised ASA.</p>		<p>information. This table should identify and provide reasons for any observed differences particularly where it appears the EU SmPC is more restrictive. The TGA can then validate the sponsor's assertion that there are no material differences between the routine risk minimisation activities undertaken in Europe compared to Australia. An adequately revised ASA should be submitted for review before this application is approved.</p>

Summary of recommendations

It is considered that the sponsor's response to the TGA's consolidated request for further information has not adequately addressed all of the issues identified in the RMP evaluation report (see below).

Outstanding issues

Issues in relation to the RMP

The sponsor was advised to correct the pagination in the 'Table of Contents' of the ASA and to apply appropriate document control to the ASA. The sponsor states: *'No change has been made to the ASA initially submitted to the TGA, therefore the ASA Table of Content does not need to be updated.'* Unfortunately it appears the sponsor has not checked the pagination in the 'Table of Contents' of the ASA and not identified the observed inconsistencies. Consequently this issue remains outstanding and a corrected ASA, which should be appropriately version controlled and dated, must be provided to the TGA for review before this application is approved.

The sponsor was asked to provide compelling justification for the deletions/omissions from the summary of the Ongoing Safety Concerns in comparison to what was previously accepted for Saflutan. Alternatively if the sponsor decided to include these ongoing safety concerns in Australia for Taptiqom, then consideration must be given as to what pharmacovigilance and risk minimisation activities will be proposed for them and the ASA should be revised accordingly. The sponsor has responded as follows:

- In regard to the important potential risk: 'Embryotoxicity', the sponsor concedes: *'Embryotoxicity has been seen in animal testing with tafluprost.'* However, then states: *'After reassessing the risks for tafluprost, embryotoxicity was not considered anymore as an important potential risk for humans'* without providing detail of any such reassessment or new evidence. This response is considered inadequate and it is recommended that the important potential risk: 'Embryotoxicity' should be included as a new ongoing safety concern for Taptiqom, and consideration given as to what pharmacovigilance and risk minimisation activities will be proposed for it. These changes need only be reflected in a revised ASA before this application is approved.
- In regard to the important potential risk: 'Possible drug interaction; combination of tafluprost and other prostaglandin analogues', the sponsor states this ongoing safety concern *'is mentioned as an important potential risk only in the tafluprost RMP and it is not in line with the tafluprost EU SmPC: 'No interactions are anticipated in humans, since systemic concentrations of tafluprost are extremely low following ocular dosing. Therefore, specific interaction studies with other medicinal products have not been performed with tafluprost.'* However, this possible drug interaction is in the context of reports of paradoxical elevations in intraocular pressure. Consequently the sponsor's reassessment of this risk is considered inadequate and it is recommended that the important potential risk: 'Possible drug interaction; combination of tafluprost and other prostaglandin analogues', should be included as a new ongoing safety concern for Taptiqom, and consideration given as to what pharmacovigilance and risk minimisation activities will be proposed for it. These changes need only be reflected in a revised ASA before this application is approved.
- In regard to the important missing information: 'Patients with aphakia', 'Patients with neovascular, angle closure, narrow angle, pseudoexfoliative or congenital glaucoma' & 'Patients wearing contact lenses', the sponsor states: *'Tafluprost EU SmPC ('There is no experience with tafluprost in neovascular, angle-closure, narrow-angle or congenital glaucoma. There is only limited experience with tafluprost in aphakic patients and in pigmentary or pseudoexfoliative glaucoma') and RMP are in line with each other. The statement was mistakenly left out from Taptiqom RMP and will be considered as missing information. Taptiqom RMP will be corrected accordingly. Since the Australian PI is consistent with the EU SmPC, and this statement will be included in the EU RMP, the ASA will not be updated. We provide an assurance that an updated RMP will be provided to the TGA at the next opportunity.'* In general this response is acceptable, except for the absence of any comment on the important missing information: 'Patients wearing

contact lenses' and the sponsor's refusal to amend the ASA accordingly. Consequently this issue remains outstanding until the important missing information: 'Patients with aphakia', 'Patients with neovascular, angle-closure, narrow angle, psuedoexfoliative or congenital glaucoma' & 'Patients wearing contact lenses' are included as ongoing safety concerns as reflected in a revised ASA and consideration given as to what pharmacovigilance and risk minimisation activities will be proposed for them.

The sponsor was advised that Table 1- 'Summary of the Australian Risk Minimisation Plan' of the ASA may need to be revised if additional ongoing safety concerns are included. As mentioned above the sponsor has declined to do so. However, as discussed above this is considered inadequate. Consequently this remains an outstanding issue and an adequately revised ASA should be submitted for review before this application is approved. In addition this table should be re-titled 'Summary of the Australian Risk Management Plan', as it refers to both pharmacovigilance and risk minimisation activities.

The sponsor was asked to identify and provide reasons for any differences between the risk minimisation activities undertaken as reflected in the content of the EU SmPC and the proposed Australian PI in a revised ASA. The sponsor states: *'The differences between the PI and the SmPC are minor and have no impact on the level of safety profile as described in the RMP and ASA. Therefore no change has been made to the ASA.'* This is not entirely satisfactory. Consequently it is recommended that the ASA should include a risk minimisation activities table, which compares the actual content and wording of the current EU SmPC and the proposed Australian PI & CMI for all of the specified ongoing safety concerns and missing information. This table should identify and provide reasons for any observed differences particularly where it appears the EU SmPC is more restrictive. The TGA can then validate the sponsor's assertion that there are no material differences between the routine risk minimisation activities undertaken in Europe compared to Australia. An adequately revised ASA should be submitted for review before this application is approved.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration

RMP

No wording can be suggested until the ASA has been adequately and appropriately revised and updated (see above).

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The pharmaceutical chemistry evaluator had no objections to registration.

The product is for ocular use and is intended to act without systemic absorption; therefore, no bioavailability data were required and none were submitted.

The product contains no unusual excipients for this dosage form.

The Microbiology Section at the TGA has stated that the microbiological and sterility aspects are acceptable.

Nonclinical

The nonclinical evaluator had no objections to registration.

- The ocular absorption of tafluprost and timolol was comparable or slightly lower with co-administration compared to dosing with each agent alone in rabbits. No systemic pharmacokinetic interaction was evident in monkeys.
- No novel or exacerbated toxicity was observed with the combination compared to the single agents in a 3 month study in monkeys involving twice daily dosing with eye drops containing the drugs at the proposed clinical strength or 3-times higher. Acceptable ocular tolerance was shown in a study in rabbits conducted with the commercial formulation.

Clinical

The clinical evaluator had no objections to registration.

Pharmacokinetic and pharmacodynamic studies

Both tafluprost and timolol have low systemic bioavailability when given as eye drops. Neither compound influences the PK of the other. In combination, the two products have an additive pharmacodynamic effect.

Phase III studies (efficacy)

Study 201050 was conducted at 60 centres in 10 countries (Belgium, Estonia, Finland, Germany, Israel, Italy, Netherlands, Poland, Russia and United Kingdom) between February 2011 and September 2012. See Table 4 below for study design details.

Table 4: Study 201050 design

Design	Parallel Double masked 2-week run-in 4-week wash-out
Patients	18+ years Ocular hypertension or open-angle glaucoma On monotherapy (prostaglandin or timolol) for at least 2 weeks and requiring additional IOP lowering medications
Intervention	FDC Tafluprost/timolol
Comparator	Timolol monotherapy or Tafluprost monotherapy
Primary endpoint	Change from baseline in average diurnal IOP at 3 months
Secondary endpoints	Proportion of responders (change from baseline IOP of 20%+) Change from baseline IOP at 2 and 6 weeks; and 6 months

Ocular diagnosis and medical history were similar across the treatment groups. About 60% of study participants were women; the age range was 23 to 87 years. Results are summarised in the Table 5 below.

Table 5: Study 201050 results

	FDC versus timolol	FDC versus tafluprost
Primary endpoint Change from baseline in diurnal IOP at 3 months	-0.885 95% CI [-1.745, -0.044] p=0.044	-1.516 95% CI [-2.044, -0.988] p<0.001
Selected other endpoints 20%+ decrease at 3 months	86% versus 77% p=0.110	89% versus 78% p=0.002
Change from baseline in diurnal IOP at 6 months	-0.838 95% CI [-1.522, -0.154] p=0.017	-1.118 95% CI [-1.626, -0.610] p<0.001

Study 201051 was conducted at 35 centres in 7 countries (Austria, Bulgaria, Czech Republic, Hungary, Latvia, Portugal and Spain) between March 2011 and May 2012. The study design is summarised in Table 6 below.

Table 6: Study 201051 design

Design	Parallel Double masked 2-week run-in wash-out; variable duration depending on prior treatment
Patients	18+ years Ocular hypertension or open-angle glaucoma Clinical need for additional IOP lowering medication
Intervention	FDC tafluprost/timolol
Comparator	Combination therapy with the mono products: timolol and tafluprost
Primary endpoint	Change from baseline in average diurnal IOP at 6 months Non-inferiority margin: 1.5 mmHg
Secondary endpoints	Proportion of responders (change from baseline IOP of 20%+) Change from baseline IOP at 2 and 6 weeks; and 3 months

Ocular diagnosis and medical history were similar across the treatment groups. About 60% of study participants were women and the age range was 19 to 85 years. The following table summarises the results.

Table 7: Study 201051 results

	FDC versus combination of mono products
Primary endpoint Change from baseline in diurnal IOP at 6 months ITT	0.315 95% CI [-0.187, 0.817]
PP	0.308 (-0.194, 0.810)

Safety

No new safety issues were identified for this FDC. The safety profile is similar to that for the mono products administered concomitantly.

Clinical evaluator's recommendation

The clinical evaluator would have no objection to the approval of Taptiqom (tafluprost 15 micrograms/mL and timolol [as maleate] 5 mg/mL) for the indication of:

Taptiqom is indicated for the reduction of intraocular pressure (IOP) in adult patients with open angle glaucoma or ocular hypertension when concomitant therapy is appropriate.

Risk management plan

Important identified risks, important potential risks and missing information are a combination of those for the mono products.

Risk-benefit analysis**Delegate's considerations**

The FDC is more effective in reducing intraocular pressure than each of the two mono products alone and is non-inferior to concomitant use of the mono products. The FDC product does not pose any new safety concerns over those posed by concomitant use of the two mono products.

Additional information required from sponsor prior to the Advisory Committee on Prescription Medicines (ACPM) meeting

- Update the overseas registration status.
- Provide the latest version of the EU Summary of Product Characteristics (SmPC) negotiated with the EMA.
- Provide the EMA evaluation report.

Proposed action

The Delegate had no reason to say, at this time, that the application for the FDC product Taptiqom should not be approved for registration.

Conditions of registration

Implement the latest EU-RMP with the latest updated ASA.

Request for ACPM advice

Is the ACPM satisfied that efficacy and safety have been satisfactorily established for this FDC?

Response from sponsor

Merck Sharp & Dohme (MSD) concurs with the recommendation of the TGA Delegate that Taptiqom, a new fixed dose combination (FDC) product containing the already registered active ingredients tafluprost and timolol, can be registered. Other similar ophthalmic combinations of a prostaglandin and a beta blocker are already registered.

Based on the feedback from the Delegate to align the indication to be consistent with other similar fixed dose combination products, the following indication is proposed.

Taptiqom is indicated for the reduction of intraocular pressure (IOP) in adult patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to beta blockers or prostaglandin analogues and require a combination therapy.

The clinical efficacy and safety studies considered that this was a combination of two already registered products that would be used at the same approved doses as the monotherapy product. The primary aim was to demonstrate that the fixed dose combination of tafluprost and timolol was superior in lowering IOP compared with the individual components. In addition it was shown that IOP lowering effect of the FDC given

once daily was non-inferior to the effect provided by the components given concomitantly (tafluprost once daily plus timolol twice daily). The conclusion reached by the Delegate is that *'the FDC is more effective in reducing intraocular pressure than each of the two mono products alone and is non-inferior to concomitant use of the mono products. The FDC product does not pose any new safety concerns over those posed by concomitant use of the two mono products.'* The putative advantage of the FDC of tafluprost and timolol is to reduce the washout effect of administering multiple drops to the eye and to increase compliance. This product is also preservative free.

Proposed changes to the PI have been addressed and outstanding matters related to the RMP will be addressed directly with the Delegate.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new combination of active ingredients for currently registered products.

The ACPM resolved to recommend to the TGA Delegate of the Minister and Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Taptiqom 15/5 eye drops, solution containing tafluprost 15 µg/mL and timolol (as maleate) 5 mg/mL to have an overall positive benefit-risk profile for the indication:

Taptiqom is indicated for the reduction of intraocular pressure (IOP) in adult patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to beta blockers or prostaglandin analogues and require a combination therapy.

Proposed conditions of registration

- Negotiation of Product Information and Consumer Medicines Information to the satisfaction of the TGA.
- Satisfactory implementation of the Risk Management Plan most recently negotiated by the TGA.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:

- The recommendation to occlude tear ducts after instillation be emphasised
- Amendment of the CMI under 'additional side effects timolol maleate' the ACPM recommended 'slowing of your heart rate' and 'shortness of breath' be moved up to the 2nd and 3rd line.

Specific Advice

The ACPM advised, in response to the Delegate's specific question on this submission, that it was satisfied that efficacy and safety had been satisfactorily established for this fixed dose combination.

Outcome

The sponsor formally requested in their pre-ACPM response dated 14 November 2014 that the proposed trade name Taptiqom be changed to Taptiqom 15/5 to reflect the strengths of the two active ingredients in the product.

Based on a review of quality, safety and efficacy, TGA approved the registration of Taptiqom 15/5 tafluprost 15 microgram/mL and timolol (as maleate) 5 mg/mL single dose eye drop solution ampoule, indicated for:

Taptiqom 15/5 is indicated for the reduction of intraocular pressure (IOP) in adult patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to beta blockers or prostaglandin analogues and require a combination therapy.

Specific conditions of registration applying to these goods

The Taptiqom 15/5 (tafluprost/timolol maleate) EU Risk Management Plan (RMP), Version 1 dated 29 April 2013 with Australian Specific Annex Version 1.1, dated January 2015, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product information

The Product Information approved for Taptiqom 15/5 at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

Attachment 2. Extract from the clinical evaluation report

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