



Australian Government

Department of Health

Therapeutic Goods Administration

# Australian Public Assessment Report for fenofibrate

Proprietary Product Name: Lipidil

Sponsor: Abbott Australasia Pty Ltd

**December 2014**

**TGA** Health Safety  
Regulation

## About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- 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 <<http://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 common abbreviations

Abbreviation	Meaning
ACCORD	Action to control cardiovascular risk in diabetes
ACR	Albumin/creatinine ratio
BCVA	Best corrected visual acuity
BMI	Body mass index
CSME	Clinically significant macular oedema
CI	Confidence interval
CVD	Cardiovascular disease
DB	Double-blind
DBP	Diastolic blood pressure
DME	Diabetic macular oedema
DR	Diabetic retinopathy
ETDRS	Early treatment diabetic retinopathy study
FIELD PSP-DR	Fenofibrate intervention and event lowering in diabetes primary and secondary prevention of diabetic retinopathy
HbA1c	Glycaeted haemoglobin
HDL	High density lipoprotein
HE	Hard exudates
HR	Hazard ratio
ITT	Intent-to-treat
LDL	Low density lipoprotein
N/A	Not available
NNT	Number needed to treat
NPDR	Non proliferative diabetic retinopathy
OCT	Optical coherence tomography

Abbreviation	Meaning
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
TC	Total cholesterol
T2DM	Type 2 diabetes mellitus
TZD	Thiazolidinedione

## I. Introduction to product submission

### Submission details

<i>Type of submission</i>	Extension of Indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	8 October 2013
<i>Active ingredient:</i>	Fenofibrate
<i>Product name:</i>	Lipidil
<i>Sponsor's name and address:</i>	Abbott Australasia Pty Ltd Sir Joseph Banks Corporate Park 32-34 Lord Street Botany NSW 2019
<i>Dose form:</i>	Film coated tablet
<i>Strengths:</i>	48 mg and 145 mg
<i>Container:</i>	Blister pack
<i>Pack sizes:</i>	48 mg – 60 tablets 145 mg - 10 and 30 tablets
<i>New approved therapeutic use:</i>	<i>Lipidil is indicated for the reduction in the progression of diabetic retinopathy in patients with Type 2 diabetes and existing diabetic retinopathy. Lipidil does not replace the appropriate control of blood pressure, blood glucose and blood lipids in reducing the progression of diabetic retinopathy.</i>
<i>Route of administration:</i>	Oral
<i>Dosage:</i>	1 x 145 mg tablet Although 3 x 48 mg tablets are equivalent to 1 x 145 mg tablet, the 48 mg tablets are only recommended when a decreased dosage is required
<i>ARTG numbers:</i>	118642, 118634

### Product background

Diabetic retinopathy (DR) is a leading risk factor and cause of blindness worldwide. Tight glucose and blood pressure (BP) control has been shown to significantly decrease risk of development as well as progression of retinopathy and represents the cornerstone of medical management of DR. The two most threatening complications of DR are diabetic macular oedema (DME) and proliferative DR (PDR). Current treatment of DME and PDR

mostly relies on laser photocoagulation. However, some patients suffer permanent visual loss as a result of laser therapy (including loss of peripheral vision and night vision). Furthermore, DR progresses in some patients despite current therapy. Also, pathology involving central vision cannot be treated with laser therapy. There is a clinical need for an early intervention that can delay progression of DR.

Fenofibrate is a fibric acid derivative with lipid modifying effects reported in humans, mediated via activation of the Peroxisome Proliferator Activated Receptor type alpha (PPAR $\alpha$ ). Fenofibrate marketed since 1975 (France) is currently approved in Australia as an adjunct to diet in the treatment of hypercholesterolaemia; Type II, III, IV and V dyslipidaemia and dyslipidaemia associated with Type 2 diabetes mellitus (T2DM), with or without statin therapy.

The application to extend the indications for fenofibrate was based on the clinical data obtained in patients with T2DM treated with fenofibrate from two placebo controlled ophthalmologic Sub-studies - Fenofibrate Intervention and Event Lowering in Diabetes Primary and Secondary Prevention of Diabetic Retinopathy (FIELD PSP-DR) and Action to Control Cardiovascular Risk in Diabetes-Eyes Study (ACCORD-Eye). These data support the update of the Product Information (PI) document to include information on treatment of DR and addition to the indications of fenofibrate to include, "Reduction in the progression of DR in patients with T2DM in addition to appropriate control of glycaemia and BP".

The **current** full indications include:

*Lipidil is indicated as an adjunct to diet in the treatment of:*

- *hypercholesterolaemia;*
- *Types II, III, IV and V dyslipidaemia;*
- *dyslipidaemia associated with Type 2 diabetes.*

This AusPAR describes the application by Abbott Australasia Pty Ltd (the sponsor) to extend the indications for Lipidil to include the following proposed new indication:

*Lipidil is indicated for the reduction in the progression of diabetic retinopathy in patients with Type 2 diabetes and existing diabetic retinopathy. This applies in addition to usual therapy of Type 2 diabetes.*

### **Regulatory status**

Fenofibrate 145 mg (nanoparticles formulation) was registered in Australia in 2004. It is bioequivalent to fenofibrate 200 mg micronised (capsule) and 160 mg (tablet).

Fenofibrate is currently only registered for DR in the Ukraine.

An extension of the indication to slow the progression of DR has not been submitted to any other regulatory agency.

### **Product Information**

The approved PI current at the time this AusPAR was prepared can be found as Attachment 1.

## II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

## III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

## 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.

### Clinical rationale

This application evaluates the clinical data obtained in patients with T2DM treated with fenofibrate and fenofibric acid in order to support the update of the Summary of Product Characteristics (SmPC) to include information on treatment of diabetes eye complications, such as reduction in the progression of DR in patients with T2DM.

**Comment:** Fenofibrate is used in dyslipidaemia and this application is to extend its use to DR. DR is a major complication of diabetes. From the ACCORD-Eye Study, the evidence shows that fenofibrate is useful for slowing progression of DR in diabetics with mild to moderate DR at baseline. It was not particularly effective among patients without DR at baseline. The FIELD PSP-DR Study also shows that fenofibrate is not effective in diabetic patients with no DR at baseline, while there was proven benefit in the study for the minority of diabetic patients who had some DR at baseline. Patients in the ACCORD-Eye Study had diabetes that was more long-standing and also more likely to have mild to moderate DR at baseline.

The proposed indication for this drug is to slow DR progression. The disease process involved is the effect of diabetes in causing a complication of DR, which becomes progressively worse. The claim is not to cure DR, but to slow the rate of progression, which is measured by changes in Early Treatment Diabetic Retinopathy Study (ETDRS) steps as outlined in the TGA guidelines.

### Scope of the clinical dossier

The submission contained the following clinical information:

- Tabular listing of all clinical studies
- Clinical study reports
- Reports of efficacy and safety studies [for the indication 'dyslipidaemia']
- Study reports of controlled clinical studies pertinent to the claimed indication
- Literature references



**Paediatric data**

No new information available.

**Good clinical practice**

No new information available.

**Table 1: Tabular Listing of All Clinical Studies**

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Phase III Efficacy	FIELD PSP-DR		Evaluate the benefit of five years of treatment with fenofibrate on the prevention of occurrence or progression of DR	Randomised, double-blind, placebo-controlled (conducted in a subgroup of the FIELD Study population)	Fenofibrate, 200 mg, once daily, oral	1012 (Full analysis set)	T2DM	5 years	Complete, Full
Phase II Efficacy	S348.2.001		Evaluate the effects of fenofibric acid (SLV348) on changes of DME	Randomised, prospective, double-blind, placebo-controlled	Fenofibric acid, 135 mg, once daily, oral	110	T2DM with Diabetic DME	12 months	Complete, Full
Phase III Efficacy	ACCOR D-Eye		Evaluate the benefit of fenofibrate versus placebo both co-administered with	Double-blind randomised placebo controlled	Fenofibrate 160 mg tablet, once daily, oral	1593	T2DM	4 years	Complete, Publication

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
			simvastatin in limiting the progression of DR						

### Pharmacokinetics

#### Studies providing pharmacokinetic data

No new information available.

#### Evaluator's overall conclusions on pharmacokinetics

No new information available.

### Pharmacodynamics

#### Studies providing pharmacodynamic data

No new information available.

#### Evaluator's overall conclusions of pharmacodynamics

No new information available.

### Dose selection for the pivotal trials

ACCORD-Eye Study: 160mg tablet

FIELD PSP-DR Study: 200 mg micronised capsule

**Comment:** While the sponsor claims bioequivalence between the 160 mg, 200 mg and 145 mg (145 mg is available in Australia), the sponsor does not present any documents proving bioequivalence.

## **Efficacy**

### **Studies providing efficacy data**

#### ***ACCORD-Eye – A supportive study***

ACCORD-Eye is a pre-specified sub-study of the main ACCORD trial. Its primary aim was to determine whether any of the three interventions (glycaemia, lipid and BP) evaluated in the main ACCORD Trial reduced the risk of development or progression of DR, as compared with the respective standard treatments<sup>1,2</sup>.

ACCORD-Eye was submitted as a publication and in two summary documents but not as a full regulatory package, and neither the ACCORD publication nor the regulatory package for ACCORD was submitted. If these submissions were present ACCORD-Eye would be a pivotal study rather than a supportive study.

#### ***FIELD – the pivotal study***

FIELD PSP-DR is a pre-specified and planned sub-study as part of the FIELD Trial. This double-blinded, placebo-controlled study had as a primary objective to evaluate the benefit of five years (on average) of treatment with 200 mg micronised fenofibrate on the occurrence or progression of DR in T2DM subjects using ETDRS classification of fundus pictures.

#### ***S348.2.001 – a supportive phase 2 study***

Study S348.2.001 was conducted in order to assess the effect of fibrate treatment in subjects with a more advanced stage of DR (moderate to severe non-proliferative DR (NPDR) or mild PDR).

The evaluator did not consider this study to be statistically significant.

### **Evaluator's conclusion on clinical efficacy**

The evidence indicates that only diabetic patients with some prior DR, whether mild or moderate may benefit at all from fenofibrate. An argument can be made that fenofibrate is more clinically efficacious in patients with moderately elevated low-density lipoprotein (LDL) (2.2 – 2.9 mmol/L) and triglyceride lipase (TGL) (3.3 – 5.2mmol/L).

There have been no analyses that have been subcategorised by thiazolidinedione (TZD)<sup>3</sup> usage, nor are there reports that such patients with such usage have been excluded or whether the trial has been designed to balance TZD usage among patients. It is assumed with randomisation, that TZD usage should be balanced between treatment and placebo arms. If the sample size was sufficient to balance for TZD usage then the effects of fenofibrate would be beyond any interaction with TZD usage. However it would be interesting to see the breakdown of TZD usage in the treatment and placebo arms of the FIELD PSP-DR and ACCORD-Eye Sub-studies.

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<sup>1</sup>The ACCORD study group and ACCORD-Eye study group. Effects of medical therapies on retinopathy progression in type 2 diabetes. N. Engl. J. Med., 2010, 363:233-244

<sup>2</sup>Chew E, Ambrosius WT, Howard LT. Rationale, Design and methods of the Action to control Cardiovascular Risk in Diabetes Eyes Study (ACCORD-Eye). Am. J. Cardiol, 2007, 99: S103-S111.

<sup>3</sup>The thiazolidinediones (TZDs) are a class of medications used in the treatment of T2DM. They were introduced in the late 1990s. TZDs act by activating peroxisome proliferator-activated receptors

Also in the submission package the actual ACCORD Study was not submitted, but the ACCORD-Eye publication was submitted.

As reported previously their use of the ETDRS scale as an outcome of primary efficacy was questionable as an ETDRS change by three steps is clinically significant in patients with prior DR and two steps is clinically significant in patients with no DR at baseline.

Both studies showed no difference in patients with no DR at baseline and a notable difference in patients with prior DR, but often the reported measures were assessing a 2-step change. However, 3-step changes were also reported but not in the main efficacy table. This is a minor issue as a 3-step change was found to be statistically significant in patients with prior DR.

A summary was presented for the ACCORD-Eye Study, whereas a regulatory package was submitted for the FIELD PSP-DR Study and the S.348.2001 Study using biomarkers. The FIELD PSP-DR Study was pivotal, the biomarker study and ACCORD-Eye were supportive in that they showed no effect of fenofibrate in patients with PDR or pre-proliferative DR with DME. Had the regulatory package been submitted for the ACCORD-Eye package, it would have been a pivotal study.

## **Safety**

### **Studies providing evaluable safety data**

FIELD PSP-DR has safety data. ACCORD-Eye does not have a safety submission.

### **Summary of patient/drug exposure**

Comment: There were no major issues in safety.

### **Deaths and other serious adverse events**

**Comment:** There was a statistically non-significant ( $P=0.3$ ) increase in coronary deaths in patients taking fenofibrate from three deaths out of 500 in the placebo arm and six deaths in the treatment arm. Similarly, this was the case for all cardiovascular disease (CVD) mortality ( $P=0.14$ ).

### **Evaluator's overall conclusions on clinical safety**

There are no statistically significant differences in endpoint relating to safety, other than a rise in creatinine. This rise in creatinine by  $11 \mu\text{mol/L}$ , over four to five years, is beyond the rise seen in placebo. Alternative doses have been recommended for renally compromised patients.

### **First round benefit-risk assessment**

#### **First round assessment of benefits**

Three studies were provided as regulatory packages. FIELD PSP-DR and ACCORD-Eye are consistent bases on a statistically non-significant value for the Cochrane Q Test for heterogeneity. The third study is completely different as it uses biochemical markers and

follow-up is for one year whereas patients with moderate to severe DR were exclusively selected.

It is difficult to comment on internal and external validity as the inclusion and exclusion criteria were not given. However from the submission, in the ACCORD-Eye Study patients with severe DR were excluded, hence there is no evidence to generalise fenofibrate to patients with severe DR.

The benefits of fenofibrate in the proposed usage are:

- It is effective in the subset of diabetic patients with some prior DR.
- It is especially effective in diabetic patients with dyslipidaemia as per LDL (LDL 2.2-2.9 mmol/L). However, this may just reflect the cut-offs they have chosen for this variable.
- It is also especially effective in diabetic patients with triglycerides (TG) between 3.3-5.2 mmol/L. This may also reflect the cut-offs they have chosen for this variable.

This clinical benefit is seen on top of the use of a concurrent statin.

### **First round assessment of risks**

The risks of fenofibrate in the proposed usage are:

- It can be considered ineffective polypharmacy to treat patients with diabetes that show no DR.
- By delaying the use of fenofibrate to diabetic patients, the potentially unnecessary side effects, adverse drug reactions and drug interactions of fenofibrate are avoided. This includes the waste of resources in providing fenofibrate in population where it is not effective (diabetics without prior DR).

### **First round assessment of benefit-risk balance**

The benefit-risk balance of fenofibrate is unfavourable given the proposed usage, but would become favourable if the changes recommended under First round recommendation regarding authorisation are adopted.

### **First round recommendation regarding authorisation**

Fenofibrate should be used in diabetic patients who display mild to moderate DR to slow the progression of DR. Fenofibrate is especially useful in those patients with LDL in the range of 2.2-2.9 mmol/L or TG in the range of 3.3-5.2mmol/L and shows beneficial effects in slowing progression of DR on top of concurrent statin therapy.

ACCORD-Eye was a study that showed statistically and clinically significant effects in diabetic patients with prior DR. In this study patients in both arms were co-administered with statin therapy, therefore fenofibrate with concurrent statin therapy is recommended.

From the evidence it can be seen that two independent studies have shown that patients with prior DR benefit from fenofibrate. These results are both statistically significant; therefore pooling the studies in this respect would also yield statistically significant results. These studies are non-heterogeneous as the Cochrane Q test for heterogeneity was statistically non-significant.

Also it does not make sense to pool the overall studies and say fenofibrate is a statically and clinically significant treatment for all diabetics regardless of prior DR. This is because

in both studies the patients without DR at baseline did not receive any clinical benefit in terms of slowing progression of DR.

Furthermore FIELD PSP-DR was not significant, whereas ACCORD-Eye was; the main reason likely to be that a higher proportion of ACCORD patients had prior DR and had poorer glycaemic control.

The reasoning is that it takes time for diabetics to develop DR but once developed it will usually progress. The follow-up of both studies was not long enough for patients without prior DR to develop and also have varying rates of progression of DR.

### List of questions

No further questions.

## V. Pharmacovigilance findings

### Risk management plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR).

EU-RMP Edition 1 (dated January 2012, DLP 07/10/2011) and Australian Specific Annex (part of EU-RMP Edition 1, dated January 2012, DLP 07/10/2011).

### Safety specification

Subject to the evaluation of the clinical aspects of the Safety Specification (SS) by the Office of Medicines Authorisation (OMA), the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows (Table 2):

**Table 2: Summary of ongoing safety concerns**

Summary of ongoing safety concerns	
Important identified risks	Cholelithiasis Pancreatitis Myopathy/Rhabdomyolysis Drug-induced hepatitis Elevations in serum creatinine Photosensitivity Venous Thromboembolic disease
Important potential risks	Increased risk of Major Adverse Cardiac Events in women on combined treatment
Important missing information	No/little clinical trial information on: Children/adolescents (<18 years) Pregnant/lactating women Patients with severe renal impairment

Summary of ongoing safety concerns	
	Patients with hepatic insufficiency

**OPR reviewer comment:** Notwithstanding the evaluation of the clinical aspects of the SS, this is considered acceptable.

### Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities for important identified and potential risks and missing information (as stated above). Furthermore, one additional activity is planned for one of the risks (Table 3).

It is noted that the sponsor is planning a clinical trial (a randomised, double-blind, placebo-controlled trial evaluating the effect of Trilipix (fenofibric acid) on the incidence of major adverse cardiovascular (CV) events in high-risk men and women at LDL-cholesterol (LDL-C) goal on statin therapy, but with residually high TG and low high-density lipoprotein-cholesterol (HDL-C)) for which no protocol is available as yet.

The study may mainly apply to the fenofibrate-simvastatin fixed dose combination (FDC) and to the United States (US) Food and Drug Administration (FDA) requirement in response to the results of the ACCORD trial (Ginsberg *et al.*, 2010<sup>4</sup>), but considering that some patients will be on a therapy consisting of a statin combined with fenofibrate, the results of the study may be relevant in the context of this application. The sponsor should submit the protocol of the study and the results as soon they become available.

**Table 3: Additional pharmacovigilance activities planned by the sponsor**

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
A randomised, double-blind, placebo controlled trial evaluating the effect of Tripilex (fenofibric acid) on the incidence of major adverse CV events in high-risk men and women at LDL-C goal on statin therapy, but with residually high TG and low HDL-C.	Increased risk of Major Adverse Cardiac Events in women on combined treatment (with statins).	Evaluation of the effect of Tripilex (fenofibric acid) on the incidence of major adverse CV events in high-risk men and women at LDL-C goal on statin therapy, but with residually high TG and low HDL-C.  Trial completion planned for 31/01/2020.	Final submission report due 31/01/2021.

<sup>4</sup> Ginsberg HN et al. (ACCORD Study Group) 2010. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 362:1563–1574.

Additional activity	Assigned safety concern	Actions/outcome proposed	Estimated planned submission of final data
Protocol unavailable.			

*OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones:*

No pharmacovigilance activities beyond routine activities are proposed by the sponsor except for the proposed study mentioned above. This is considered acceptable.

### **Risk minimisation activities**

The sponsor states that no additional risk minimisation activities are necessary.

**OPR reviewer comment:** The sponsor's conclusion is acceptable.

### **Potential for medication errors**

For the purposes of this RMP evaluation different types of medication errors, as suggested by Ferner and Aronson (2006)<sup>5</sup>, have been considered.

**OPR reviewer comment:** The sponsor's actions to minimise medication errors are considered acceptable.

### **Potential for overdose**

The risk for intentional overdose is low. In the proposed PI, over-dosage and its management have been discussed to a satisfactory standard.

### **Potential for off-label use**

The information regarding indications for this drug given in the proposed Australian PI is considered acceptable.

### **Potential for paediatric off-label use**

The sponsor recognises this drug is contraindicated in children. This is reflected in the proposed PI. This is considered acceptable.

### **Risk minimisation plan**

No additional risk minimisation activities are proposed for Lipidil.

**OPR reviewer comment:** In regard to the proposed routine risk minimisation activities, the draft PI is considered satisfactory.

### **Summary of first round recommendations**

The OPR provides these recommendations in the context that the submitted RMP (EU-RMP Edition 1 (dated January 2012, DLP 07/10/2011) and Australian Specific Annex (part of EU-RMP Edition 1, dated January 2012, DLP 07/10/2011)) is supportive to the application; the implementation of an RMP satisfactory to the TGA is imposed as a

<sup>5</sup> Ferner RE, Aronson JK 2006. Clarification of terminology in medication errors: definitions and classification. *Drug Saf* 29:1011–1022.



condition of registration; the submitted EU-RMP is applicable without modification in Australia unless so qualified; and the draft PI and consumer medicine information (CMI) documents should NOT be revised until the Delegates Overview has been received:

**Further safety considerations:**

Safety considerations may be raised by the clinical evaluators through the consolidated request for further information and/or the 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 RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.

Unless the sponsor can provide compelling justification against any of the following recommendations, the following should be considered:

Recommendations in regard to the proposed indication:

1. Lipidil is contraindicated in 'severe renal dysfunction' (as outlined in the proposed Australian PI). It is noted that, in the RMP document, the sponsor defines patients with severe renal impairment as having a creatinine clearance ( $Cl_{Cr}$ ) of less than 30 mL/min, and this is a contraindication of Lipidil. But in the proposed Australian PI the sponsor makes a dosing recommendation for patients with a  $Cl_{Cr}$  of 10–20 mL/min and 20–60 mL/min. This may cause confusion in prescribers of this medicine. The sponsor should clarify this contradiction. Furthermore, the sponsor may consider quoting the relevant values using both  $Cl_{Cr}$  (in mL/min) and estimated Glomerular Filtration Rate (GFR) (in mL/min/1.73 m<sup>2</sup>).

Recommendations in regard to pharmacovigilance activities:

2. The sponsor should submit the protocol of the study 'A randomised, double-blind, placebo-controlled trial evaluating the effect of Trilipix (fenofibric acid) on the incidence of major adverse CV events in high-risk men and women at LDL-C goal on statin therapy, but with residually high TG and low HDL-C and the results as soon they become available.

Recommendations in regard to risk minimisation activities:

3. The sponsor may consider updating the CMI to reflect the new indication.

**Second round review**

A summary of the sponsor's responses to the recommendations outlined above is as follows:

**Recommendation 1:** The sponsor proposes to delete the dosing recommendation defined by  $Cl_{Cr}$  of 10-20ml/min (one 48mg tablet) in the PI.

**OPR Comment:** The sponsor should outline clearly how they define severe renal dysfunction with respect to the Australian setting. Different institutions define the severity of renal dysfunction differently.

In terms of  $Cl_{Cr}$ , severe impairment of renal function is defined as <10 mL/min by the Australian Medicines Handbook (AMH) or British National Formulary (BNF), but defined as <30 mL/min by the FDA.

In terms of GFR, severely decreased renal function would be below 30 mL/min/1.73 m<sup>2</sup>.

It may be the case that, in their RMP, the sponsor has confused  $Cl_{Cr}$  and eGFR.

If the AMH or BNF definition of severe renal impairment were to be used (and it is assumed that these are used for the Australian market), a dosing recommendation for a  $Cl_{Cr}$  of 10-20 mL/min would be appropriate.

Furthermore, the sponsor may consider quoting the relevant values as GFR additionally, as this is more familiar to most clinicians.

**Recommendation 2:** The sponsor agrees to submit the protocol of the above mentioned study when agreed with the FDA

**OPR Comment:** This is considered acceptable.

**Recommendation 3:** The sponsor proposes to update the CMI accordingly once the indication and PI has been agreed and finalised. This will be done on approval.

## VI. Overall conclusion and risk/benefit assessment

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

### Quality

There was no requirement for a quality evaluation in a submission of this type.

### Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

### Clinical

#### Overview of data

The submitted data comprised:

- 1 Phase-2 Study - S348.2.001
- 2 Phase-3 Studies - FIELD/FIELD PSP-DR and ACCORD/ACCORD-Eye

The clinical evaluator was concerned that the proposed indication was not restricted to patients with pre-existing DR. In response, the sponsor added the following after the first round evaluation:

“ and existing DR. This applies in addition to usual therapy of Type-2 diabetes.”

### Efficacy

#### **S348.2.001**

This study randomised 110 patients with T2DM, who presented with DME, to fenofibrate or placebo for 12 months. Patients were eligible if laser photocoagulation could be postponed for at least three months. The primary outcome was total macular volume, measured every three months by optical coherence tomography. The point estimates of the treatment effect favoured fenofibrate, but did not achieve statistical significance.

**Table 4: Results for S348.2.001**

		Subjects (worse eye at baseline)		All eligible eyes	
		placebo N=53	fenofibrate N=57	placebo N=77 eyes	fenofibrate N=83 eyes
Total macular volume mm <sup>3</sup>	Baseline Endpoint	8.60 (1.43) 8.46 (1.38)	8.48 (1.69) 8.19 (1.60)	8.52 (1.41) 8.38 (1.28)	8.44 (1.56) 8.11 (1.45)
	Difference between groups*	-0.25 (-0.64;0.15) P=0.219		-0.24 (-0.56;0.08) P=0.138	
2-step progression of ETDRS grade		8/45 17.8%	5/49 10.2%		
Need for laser photocoagulation		6/53 11.3%	9/57 15.8%		

\*analysis of variance for worse eye and generalised estimation equation (GEE) analysis for all eligible eyes

### ***Fenofibrate intervention and event lowering in diabetes - FIELD - & the ophthalmological sub-study FIELD PSP-DR***

FIELD was a multinational study in 63 centres (hospital or community clinics) in Australia, New Zealand and Finland. It randomised 9795 patients (50-74 years) to fenofibrate (micronised 200 mg; equivalent to Lipidil 145 mg) or placebo. The study duration was five years. Decisions about changes to diabetic therapy or other lipid-lowering therapy were at the discretion of the patient's primary-care doctor. By the end of the study, 1776 (36%) of the patients in the placebo arm were on an additional lipid-lowering therapy (mainly statins); the corresponding numbers for the fenofibrate arm were 994 (19%).

All instances of laser photocoagulation, which was a pre-specified tertiary outcome, were recorded. The requirement for first laser treatment was statistically significantly lower in the fenofibrate group than the placebo group: 164 (3.4%) versus 238 (4.9%), Absolute risk reduction (ARR) = 1.5% (95% Confidence Interval (CI): 0.7%-2.3%).

#### ***FIELD PSP-DR study***

At 22 of the FIELD centres, patients were also approached to participate in the ophthalmology sub-study, which involved serial retinal photography. Patients were

excluded if fundus photographs of either eye showed PDR, severe NPDR, clinically significant DME, or evidence of laser treatment.

Grading of retinopathy was done using ETDRS criteria (17 steps)<sup>6</sup>. The primary outcome of the sub-study was progression of DR defined as at least a 2-step increase in ETDRS grade after two years or more of follow-up. This was for the worse eye at baseline; or if of equal grade, the right eye.

Two-field colour fundus photographs of both eyes were taken at baseline and were also scheduled at two years, five years, or study close out. Grading was done by two ophthalmologists from Finland and Australia, who were blinded to treatment assignment.

1012 patients (10% of the whole study population) participated in the ophthalmological sub-study: 782/1012 (77.3%) of the study participants did not have DR at baseline; the rest had mild or moderate NPDR.

The primary endpoint of 2-step progression of retinopathy grade was not statistically significantly different between the two groups; however there was a statistically significant difference for patients with pre-existing retinopathy (14.6% versus 3.1%); the test for interaction was statistically significant (p=0.019). There was no difference in visual acuity. Laser treatment was more common in the placebo group (4.6% versus 1.0%; see Table 2).

**Table 5: FIELD PSP-DR, four to five year follow-up, 2-step progression, laser treatment, visual acuity**

	placebo	fenofibrate	p-value
2-step progression of retinopathy (primary endpoint)			
All patients	57/463 (12.3%)	46/477 (9.6%)	0.19
No pre-existing DR at baseline	43/367 (11.7%)	43/379 (11.4%)	0.87
Pre-existing DR at baseline	14/96 (14.6%)	3/98 (3.1%)	0.005
Laser treatment			
All patients	23/500 (4.6%)	5/512 (1.0%)	<0.001
No pre-existing DR at baseline	1/388 (0.3%)	1/394 (0.1%)	0.99
Pre-existing DR at baseline	22/122 (19.6%)	4/118 (3.4%)	<0.001

<sup>6</sup> The ETDRS Severity Scale has 17 steps, ranging from no retinopathy in either eye (step 1) to high-risk proliferative retinopathy in both eyes (step 17). The severity of retinopathy can be combined into four categories: absent (steps 1–3), mild to moderate non-proliferative diabetic retinopathy (NPDR) (steps 4–7), severe NPDR (steps 8–11), and advanced diabetic retinopathy (PDR, post-laser photocoagulation, or vitrectomy) (step 12 or above).

Worsening in best corrected visual acuity 3 lines or more (15+ letters at 5 year)	23/158 (14.6%)	23/164 (14.0%)	0.89
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### ***Action to control cardiovascular risk in diabetes (ACCORD) & ACCORD-Eye***

Accord was conducted across 77 sites in the US and Canada. It randomised 10,251 patients with T2DM and a glycaeted haemoglobin of 7.5% or higher to either intensive glycaemic control (<6.0%) or standard therapy (7.0-7.9%). Of these participants, 5518 with dyslipidaemia were randomly assigned in a two-by-two factorial design to receive simvastatin (to reduce LDL cholesterol) in combination with fenofibrate (to reduce triglycerides and increase HDL cholesterol) or simvastatin monotherapy. The remaining 4733 patients were randomised in a two-by-two factorial design to either intensive BP control (120mm Hg) or standard therapy (BP <140 mmHg). The primary outcome was time until myocardial infarction (MI), stroke, or CV death. Fenofibrate was used with, not after, simvastatin. That is, ACCORD did not test the efficacy of second-line fenofibrate use.

#### ***ACCORD-Eye study***

Patients were excluded if they had a history of PDR. The primary outcome was a composite: three steps on ETDRS or development of PDR requiring laser or vitrectomy. In the sample size calculation a 20% relative reduction in percentage with the composite outcome was deemed clinically important; although the baseline event rate was not reported.

ACCORD-Eye initially enrolled 3472 patients, of whom 2856 (82%) had both baseline and Year 4 follow-up data. 51% had no DR at baseline (compared to 77% in FIELD). There was a beneficial effect of fenofibrate at four years for the pre-specified primary endpoint of progression of DR (6.5% versus 10.2%, p=0.006); the adjusted Hazard Ratio (HR) (adjusted for prior CVD, centre network and glycaemia therapy) was 0.60 (0.42, 0.87). There was no treatment effect for vision loss. Of the components of the composite endpoint, only three steps on the ETDRS were statistically significant. Subgroup analysis by pre-existing NPDR showed a treatment effect only in the subgroup that had DR at baseline.

**Table 6: ACCORD-Eye, four year follow-up, Progression of DR (composite: 3-step on ETDRS or laser or vitrectomy) & moderate vision loss (three lines or more on either eye)**

<b>Intervention</b>	<b>Progression</b>	<b>Adjusted OR (95% CI)</b>	<b>p-value</b>	<b>Moderate vision loss</b>	<b>Adjusted HR (95% CI)</b>	<b>p-value</b>
Glycaemia therapy						
Intensive	104/1429 (7.3%)	0.67 (0.51,0.87)	0.003	409/1715 (23.8%)	0.88 (0.77, 1.01)	0.06
Standard	149/1427 (10.4%)			457/1737 (26.3%)		

Intervention	Progression	Adjusted OR (95% CI)	p-value	Moderate vision loss	Adjusted HR (95% CI)	p-value
Dyslipidaemia therapy						
Fenof+simva.	52/806 (6.5%)	0.61 (0.42,0.88)	0.006	227/956 (23.7%)	0.95 (0.79, 1.14)	0.57
Simva mono.	80/787 (10.2%)			233/950 (24.5%)		
Antihypertensive therapy						
Intensive	67/647 (10.4%)	1.23 (0.84,1.79)	0.29	221/798 (27.7%)	1.17 (0.96, 1.42)	0.12
Standard	54/616 (8.8%)			185/748 (24.7%)		

**Table 7: Components of composite outcome (progression of DR)**

Component	Simva mono	Simva + fenof	p-value
Three steps on ETDRS	70	41	0.003
Laser of PDR	21	13	0.145
Vitrectomy	6	5	0.732

**Table 8: Composite endpoint of progression of DR by baseline DR**

	Simva mono	Simva + fenof	p-value
All	80/787 (10.2%)	52/806 (6.5%)	0.006
Non-proliferative DR at baseline	56/412 (13.6%)	27/405 (6.7%)	0.001
No non-proliferative DR at baseline	24/375 (6.4%)	25/4.1 (6.2%)	0.924

**Comparison of FIELD/FIELD PSP-DR and ACCORD/ACCORD-Eye**

The mean age of participants in both FIELD PSP-DR and ACCORD-Eye was 62 years; however duration of diabetes was seven years for FIELD PSP-DR and 10 years for ACCORD-Eye. About one third of participants in FIELD were on a statin (36% in placebo arm, 19% in fenofibrate arm); whereas all patients in ACCORD-Eye were assigned to

simvastatin (although compliance was not 100%). The mean glycaeted haemoglobin was 7.1% in FIELD PSP-DR and 8.2% in ACCORD-Eye, although in ACCORD-Eye this varied by whether participants were in the standard or intensive glycaemia intervention. Both eye sub-studies excluded patients with PDR, but a larger percentage in ACCORD-Eye had moderate NPDR (grade 35-47): 29% versus 12%.

The endpoints were different across the studies. The main FIELD Trial did not report any laser treatment (pre-specified tertiary outcome). This is not yet available for the fenofibrate component of the main ACCORD Trial. The FIELD PSP-DR Study reported laser treatment as a secondary outcome, but ACCORD-Eye only reported on laser treatment for PDR. These are not comparable.

The primary outcome in the FIELD PSP-DR Study was a 2-step progression of DR on the ETDRS scale. This did not achieve statistical significance; although the trend was in favour of fenofibrate (9.6% versus 12.3%). It achieved statistical significance in the subgroup with DR at baseline (3.4% versus 19.6%). The primary outcome in the ACCORD-Eye Study was the composite of 3-step progression on ETDRS scale or laser for PDR or vitrectomy. This composite endpoint was statistically significant (6.5% versus 10.2%); as was the 3-step ETDRS component. The subgroup with DR at baseline showed a larger effect (6.7% versus 13.6%). The proposed PI includes an integrated analysis using the composite primary endpoint for ACCORD-Eye (3-step worsening on ETDRS, laser or vitrectomy for PDR). The sample size for FIELD PSP-DR is much smaller than that presented for 2-step worsening in ETDRS. Also, the timescales need to be clarified.

The results of both studies suggested that fenofibrate has an independent effect on slowing the progression of DR, in addition to glycaemic control. (Note: ACCORD-Eye did not show a benefit from intensive BP control [120mmHg]; perhaps suggesting a floor effect.) In ACCORD-Eye, the absolute risk reduction, in addition to intensive glycaemic control was 1.9%.

**Table 9: ACCORD-Eye, analysis for fenofibrate component, stratified by glycaemic control percentages with progression of DR (composite outcome: three steps on ETDRS, laser for proliferative retinopathy, vitrectomy)**

Glycaemic control	Fenof. + Simva	Simva mono	Absolute risk reduction
Intensive	21/400 (5.2%)	29/406 (7.1%)	1.9%
Standard	31/406 (7.6%)	51/381 (13.4%)	5.8%

In FIELD, reasonable glycaemic control was maintained for the five years of the study across both arms (HbA1C ~ 7%). The absolute risk reduction for laser treatment was 1.5%.

### Safety

The adverse-effect profile of fenofibrate is well characterised; it has been marketed for more than 40 years. Fenofibrate is generally well tolerated. The most commonly reported side effects are gastrointestinal (nausea, vomiting, diarrhoea, flatulence, abdominal pain) and dermatological (rash, pruritus, urticaria, photosensitivity reactions). Reported post-marketing adverse events include, myalgias, rhabdomyolysis, pancreatitis, reversible increases in creatinine, and (paradoxically) depressed HDL-cholesterol levels. No new safety concerns emerged from FIELD or ACCORD.

**Clinical evaluator's recommendation**

The evaluator is included to approve the sponsor's proposed new indication.

**Risk management plan**

Changes are required to the PI for the dose for renal impairment.

There were no other material RMP issues.

**Risk-benefit analysis****Delegate considerations**

Fenofibrate is a relatively safe drug that has been marketed for over 40 years. FIELD and ACCORD showed that its effects on the surrogates of TG and HDL-cholesterol do not convincingly translate in benefits for patient-relevant endpoints, such as CV events.

However, the ACCORD-Eye Study showed that fenofibrate slows the progression of DR (as measured by the pre-specified primary endpoint that was a composite based mainly on a 3-step change for ETDRS retinopathy scale). The benefit is a 7% reduction in the risk of progression of DR (over four to five years), if the patient is on standard glycaemic control; and 1.9% if the patient is on intensive glycaemic control (with the well-known caveats around the benefit-risk equation for intensive glycaemic control in some patients). Fenofibrate does not reverse DR; nor is it a treatment for DR; it slows progression.

Other evidence to support the contention that fenofibrate slows the progression of DR is probably best regarded as supportive to pre-specified primary outcome in ACCORD-Eye. In the main FIELD Study, fenofibrate was shown to reduce the requirement for laser by 1.5% over five years (3.4% versus 4.9%). In relative terms, this represented a statistically significant reduction in time to first laser of 40% (that is, HR=0.60). However, the laser endpoint was only a tertiary endpoint; and in the FIELD PSP-DR Study the pre-specified primary outcome of 2-step progression on ETDRS was not statistically significant; although the point estimate suggested a benefit. Secondary endpoints (for example, three steps on ETDRS) were statistically significant.

One unexpected aspect of this submission is that the only jurisdiction where fenofibrate is currently registered for prevention of DR is Ukraine; and there are currently no applications to other jurisdictions.

**Proposed action**

The Delegate is inclined to approve the application to extend the indications for Lipidil.

**Request for advice**

1. The main question for ACPM advice concerns the pre-specified composite endpoint used in ACCORD-Eye, which relied heavily on a 3-step progression in ETDRS, with relatively minor contributions from laser for PDR and vitrectomy (see Table 7). Does ACPM regard three steps on ETDRS as a valid and clinically meaningful endpoint for assessing the efficacy of fenofibrate in (secondary) prevention of DR?

Both FIELD PSP-DR and ACCORD-Eye used the ETDRS scale (ETDRS Final Retinopathy Severity Scale for Persons, modified and abbreviated). This scale is based on fundal



photography at baseline and follow-up (four years for ACCORD-Eye). A >3-step change on ETDRS retinopathy scale after three years of follow-up is one of the FDA recommended endpoints for trials of patients with DR [Ophthalmologica; 2000; 214:377<sup>7</sup>].

Visual acuity is the preferred measure in trials of treatment for DR (for example, trials of laser photocoagulation or anti VEGF agents). However, fenofibrate is for prevention, not treatment. Usually treatment (such as laser) would be instituted in an attempt to avoid any serious effects of progression of retinopathy on visual acuity. Both FIELD PSP-DR and ACCORD-Eye showed no effect for the outcome of visual acuity, but this was not unexpected because of differential use of laser treatment across the two groups.

Delay of laser treatment might be regarded as more relevant outcome measure and was used in the overall FIELD Study, where fenofibrate showed a clear benefit, especially in patients with pre-existing DR. Such data are not yet available for the fenofibrate component of the overall ACCORD Study and in the ACCORD-Eye Study only laser for PDR was reported (as opposed to laser for severe/moderate/mild NPDR, et cetera).

Also, decisions about use of laser were at the discretion of individual patients and their ophthalmologists. The threshold for the use of laser treatment might vary according to individual ophthalmologists and individual patients; although randomisation will account for this, to some extent.

Pending ACPM advice, I am inclined to accept three steps on ETDRS (with follow-up of at least three years) and delay of laser treatment as acceptable surrogates.

Other, specific questions for advice are:

2. The ACCORD-Eye Study assessed fenofibrate as an add-on to simvastatin. Should the indication specify the use of fenofibrate in addition to simvastatin for reduction in the progression of DR? (Not all the patients in the FIELD Trial were on a statin.)

I am inclined, pending ACPM advice, not to require that the indication include the co-administration of simvastatin. The reasons are: nearly all patients with T2DM will be offered a statin for lipid control; not all patients in the FIELD Study were on a statin; there is evidence to indicate that statins are not effective for slowing the progression of DR [for example, Eye 2012;154:6-12<sup>8</sup>, JAMA 2007;298(8):902-916<sup>9</sup>].

The mechanism of action of fenofibrate is not known, but might be via an effect separate from its effect in triglycerides and HDL-cholesterol. ACCORD-Eye was not designed to assess the independent effect of simvastatin on DR.

3. Should the indication specify that patients should already have some degree of DR? About 50% of patients in the ACCORD-Eye Study did not have DR at baseline. About 80% of the patients in the FIELD PSP-DR Study had “no or questionable retinopathy at baseline”.

<sup>7</sup> Cunha-Vaz JG 2000. Diabetic Retinopathy: Surrogate Outcomes for Drug Development for Diabetic Retinopathy. *Ophthalmologica*; 214:377–380

<sup>8</sup> Wong TY, Simó R, Mitchell P 2012. Fenofibrate-A potential systemic treatment for diabetic retinopathy? *Am J Ophthalmol*;154:6-12

<sup>9</sup> Mohamed Q, Gillies MC, Wong TY 2007. Management of diabetic retinopathy: A systematic review. *JAMA*; 298:902-16

In both ACCORD-Eye and FIELD PSP-DR, fenofibrate did not have an effect in patients who did not have DR at baseline. This is not surprising because many patients without DR at baseline will not develop DR within the duration of the study (four to five years). A much larger and longer study would be required to assess whether fenofibrate is effective in the primary prevention of DR. I am inclined, pending ACPM advice, to require that the indication specify that fenofibrate is indicated for secondary prevention only; that is, only indicated for patients with existing DR. (This change has already been made by the sponsor.)

4. Both studies excluded patients with severe MPDR and PDR at baseline. Should the indication also exclude these patients?

Because the studies excluded these patients, we do not have any direct evidence that fenofibrate is effective in reducing progression of when retinopathy is severe. However, pending ACPM advice, I am inclined not to explicitly or specifically exclude these patients in the indication because it is likely that fenofibrate is effective in the severe group; given it is effective in the mild-moderate group. The "Clinical trial" section of the PI should include a statement that FIELD and ACCORD excluded patients with severe NPDR and PDR at baseline.

5. The ACCORD-Eye Study showed that glycaemic control slowed progression of DR and that fenofibrate had an additive effect. Should the indication specify that fenofibrate does not replace glycaemic control in the slowing progression of DR?

There is good evidence from ACCORD-Eye (and other studies) that glycaemic control slows progression of DR. There is also evidence from studies other than ACCORD-Eye that BP control slows progression of DR; although ACCORD-Eye suggests that intensive control (120mmHg) does not have any extra benefits (floor effect). The current, proposed PI states 'This applies in addition to usual therapy of T2DM'. Pending ACPM advice, I am inclined to require that a more explicit statement is made along the lines of: 'Lipidil does not replace control of BP and blood glucose in reducing progression of DR.'

### ***Conditions of registration***

The following are proposed as conditions of registration:

Implement EU-RMP Edition 1 (dated January 2012, DLP 07/10/2011) and Australian Specific Annex (part of EU-RMP Edition 1, dated January 2012, DLP 07/10/2011), and any future updates as a condition of registration.

As per the recommendation in the RMP evaluation report, the sponsor must submit the protocol of the study 'A randomised, double-blind, placebo-controlled trial evaluating the effect of Trilipix (fenofibric acid) on the incidence of major adverse CV events in high-risk men and women at LDL-C goal on statin therapy, but with residually high TG and low HDL-C', and the results as soon they become available.

The sponsor must submit results for the endpoint of "any laser treatment for retinopathy" (and the separate endpoint of vitrectomy) from fenofibrate component of the main ACCORD Study as soon as they become available.

### **Response from sponsor**

#### ***Specific questions requiring ACPM advice:***

1. Does ACPM regard three steps on ETDRS as a valid and clinically meaningful endpoint for assessing the efficacy of fenofibrate in (secondary) prevention of DR?

The pre-specified composite primary endpoint in ACCORD-Eye (3-step progression on ETDRS scale, laser for PDR and vitrectomy) was highly significant in favour of fenofibrate (when added to simvastatin) in reducing progression of DR. The beneficial effects of fenofibrate were mainly driven by the reduction in 3-step ETDRS. To the Delegate's question regarding validity of the 3-step ETDRS as a measure of efficacy, Abbott would like to direct attention to a report from a symposium on ophthalmic clinical trial design and endpoints, organised by the National Eye Institute and the FDA in 2006, addressing this point<sup>10</sup>. The FDA recommended endpoints for clinical trials of DR are:

- Statistically and clinically relevant differences in visual function at more than one time point.
- Alternatively, a statistically significant difference in the percentage of patients at three years with a 3-step change on the ETDRS retinopathy scale.

This report clearly establishes the link between visual function and ETDRS retinopathy scale.

In addition, the 3-step ETDRS results from ACCORD-Eye, further validates the results from the FIELD Study which showed a decrease in the requirement for first laser photocoagulation therapy in the fenofibrate treated subjects (Absolute risk (AR) 3.4%, fenofibrate versus 4.9%, placebo). A similar benefit was observed in FIELD PSP-DR, which reported a significant difference in 2-step progression of retinopathy grade in fenofibrate treated subjects with DR at baseline (AR: 3.1%, fenofibrate versus 14.6%, placebo). The 3-step progression in ACCORD-Eye, concatenated score across both eyes, (AR 4.6% (37/806), fenofibrate versus 7.1% (56/787), placebo) is similar to the 2-step progression used in FIELD (based on "worse eye" only).

Abbott agrees with the Delegate's assessment that 3-step on ETDRS (with follow-up of at least three years) and delay of laser treatment are acceptable surrogates.

2. *The ACCORD-Eye Study assessed fenofibrate as an add-on to simvastatin. Should the indication specify the use of fenofibrate in addition to simvastatin for reduction in the progression of DR?*

To the Delegate's question regarding the need to specify that the indication include co-administration of simvastatin, Abbott would like to reiterate the Delegate's comments that:

- The FIELD Study provided similar results as in ACCORD-Eye in the absence of statin background therapy [only an average of 19% of fenofibrate treated patients in the FIELD Study received another lipid-modifying agent (predominantly statin)].
- Statin trials did not demonstrate efficacy in DR prevention or regression.

For these two main reasons, Abbott agrees with the Delegate's proposal "not to require that the indication include co-administration of simvastatin".

3. *Should the indication specify that patients should already have some degree of DR?*

As expressed by the Delegate, the proposed indication already specifies that Lipidil should be indicated for patients with existing DR.

4. *Both studies excluded patients with severe NPDR and PDR at baseline. Should the indication also exclude these patients?*

<sup>10</sup> Csaky KG, Richman EA, Ferris III FL, 2008. Report from the NEI/FDA Ophthalmic Clinical Trial Design and Endpoints Symposium. Investigative Ophthalmology & Visual Science, 49:479-489

As mentioned by the Delegate about the FIELD Study: “All instances of laser photocoagulation, which was a pre-specified tertiary outcome, were recorded. The requirement for first laser treatment was statistically significantly lower in the fenofibrate group than the placebo group: 164 (3.4%) versus 238 (4.9%), ARR. 1.5% (95%CI: 0.7%-2.3%)”. Abbott considers it is important to specify that the lower requirement for first laser treatment in the FIELD Study was for late stages of DR, namely PDR and DME. Consequently, these results are in favour of beneficial effects of fenofibrate in late stages of DR, and the company agrees to add the proposed wording in the clinical trial section of the PI. Therefore, Abbott recommends no exclusion of those patients from treatment access.

5. *Should the indication specify that fenofibrate does not replace glycaemic control in the slowing progression of DR?*

Considering there is good evidence from ACCORD-Eye (and other studies) that glycaemic control slows progression of DR and that BP control has also been shown from other studies to slow DR progression, Abbott agrees to include a statement to this effect in the PI.

*Lipidil is indicated..., in addition to appropriate control of glycaemia and BP.*

### **Clinical evaluation**

To the Delegate’s comments regarding the CV endpoints in FIELD and ACCORD: “...effects on the surrogates of TG and HDL-C do not convincingly translate in benefits for patient relevant endpoints, such as CV events” Abbott acknowledges that both studies did not meet their primary endpoint for the overall T2DM population. However, in a pre-specified sub-group analysis for the ACCORD-lipid Trial and in a post-hoc analysis for the FIELD Study they both showed positive endpoints in the subgroup of subjects with dyslipidaemia (elevated TG and low HDL-C). In ACCORD Lipid, in the pre-specified subgroup of dyslipidaemic patients defined as lowest tertile of HDL-C ( $\leq 34$  mg/dl or 0.88 mmol/L) and highest tertile of TG ( $\geq 204$  mg/dl or 2.3 mmol/L) at baseline, fenofibrate plus simvastatin therapy demonstrated a 31% relative reduction ( $p=0.03$ ) compared to simvastatin monotherapy for the composite primary outcome (non-fatal MI, non-fatal stroke, and CV death). This is reflected in the proposed text in the Clinical Trials section of the proposed PI. In addition, the same magnitude of effect was obtained in the FIELD Study in the dyslipidaemic subgroup, HR: 0.73, 95% CI (0.58–0.91),  $p<0.05$ , and 31% reduction after adjustment for statin confounding.

### **Conditions of registration**

1. Implement EU-RMP Edition I (dated January 2012, DLP 07/10/2011) and Australian Specific Annex (part of EURMP Edition I, dated January 2012, DLP 07/10/2011), and any future updates.
2. The sponsor must submit the protocol of the study 'A randomised, double-blind, placebo-controlled trial evaluating the effect of Trilipix (fenofibric acid) on the incidence of major adverse CV events in high-risk men and women at LDL-C goal on statin therapy, but with residually high TG and low HDL-C', and the results as soon they become available.
3. The sponsor must submit results for the endpoint of "any laser treatment for retinopathy" (and the separate endpoint of vitrectomy) from fenofibrate component of the main ACCORD Study as soon as they become available.

Abbott agrees to the Conditions of Registration noted above. Please note that since separation of Abbott and AbbVie in January 2013, Abbott is no longer the sponsor of the proposed study (Point 2, above).

### ***Questions to the sponsor***

1. *Why has an application to extend the indication for fenofibrate to reduce the progression of DR (or similar) not been submitted to regulatory agencies in other jurisdictions?*

Australia was the first country where Abbott applied for this new indication. Since submission of the dossier in Australia, Abbott has submitted a variation application in EU countries using the Mutual Recognition Procedure in June 2013. Germany is the Reference Member State and the following countries are involved as Concerned Member States: Austria, Belgium, Czech Republic, Finland, France, Greece, Hungary, Ireland, Italy, Luxemburg, Portugal, Poland, Slovakia and Spain. Evaluation of this application is ongoing. It is planned to submit this dossier in other countries/areas when an initial registration will be granted.

2. *Has the sponsor had any discussions with the EMA, FDA, or any other regulatory agency about extending the indications for fenofibrate to reducing the progression of DR (or similar); and if so, what was the feedback?*

Prior to submission in the European Union (EU), a scientific advice meeting was requested with BfArM (German Federal Institute for Drugs and Medical Devices) in Germany (Reference Member State for the fenofibrate MRP). On the recommendation of BfArM, Abbott subsequently requested a centralised scientific advice meeting with the European Medicines Agency (EMA).

3. *What is the evidence to support the use of ETDRS as a surrogate for vision loss?*

A report from a symposium on ophthalmic clinical trial design and endpoints organised by the National Eye Institute and the FDA in 2006 addresses this point. The FDA recommended endpoints for clinical trials of DR are:

- a. Statistically and clinically relevant differences in visual function at more than one time point.
- b. Alternatively, a statistically significant difference in the percentage of patients at three years with a 3-step change on the ETDRS retinopathy scale.

This establishes the link between visual function and ETDRS retinopathy scale.

4. *When will the results for the endpoint of "any laser treatment for retinopathy" (and the separate endpoint of vitrectomy) from fenofibrate component of the main ACCORD Study become available?*

Communications with the United States National Institute of Health (NIH) have established that there are no current plans to analyse and publish the data on microvascular complications for the main ACCORD-Lipid population.

### ***Conclusion***

Abbott Australasia requests the ACPM, in agreement with the Delegate's expressed inclination, to recommend this revised indication for Lipidil for approval on the basis that the data and information provided:

- Meet the necessary regulatory guidelines
- demonstrate that fenofibrate slows the progression of DR in patients with T2DM

- demonstrate that fenofibrate fills an unmet clinical need for early treatment of DR in T2DM patients
- raised no objections from the Clinical and OPR evaluators
- adequately addressed the questions raised by the Delegate.

Abbott Australasia looks forward to the opportunity to complete the negotiation of a mutually agreeable PI document to support the registration of the following additional indication for Lipidil 145 mg and 48 mg tablets:

*“Lipidil is indicated for the reduction in the progression of diabetic retinopathy in patients with Type 2 diabetes and existing diabetic retinopathy, in addition to appropriate control of glycaemia and blood pressure.”*

### **Advisory committee considerations**

The ACPM having considered the evaluations and the Delegate’s overview, as well as the sponsor’s response to these documents, advised the following:

Taking into account the submitted evidence of efficacy, safety and quality, Lipidil film coated tablets containing 48 mg and 145 mg of fenofibrate have an overall positive benefit–risk profile for the following indication;

*LIPIDIL is indicated for reduction in the progression of diabetic retinopathy in patients with Type 2 diabetes and existing diabetic retinopathy. Lipidil does not replace control of blood pressure, blood glucose and blood lipids in reducing the progression of diabetic retinopathy.*

### **Proposed Product Information/Consumer Medicine Information amendments**

The ACPM endorsed the amendments recommended by the Delegate and specifically advised on the inclusion of:

- A statement in the relevant sections of the PI and CMI advising that fenofibrate has not been shown to reduce coronary heart disease morbidity and mortality in patients with T2DM.
- A statement in the Clinical Trial section of the PI and relevant sections of the CMI outlining that the benefit of fenofibrate has only been evidenced in combination with simvastatin.
- All changes to the PI identified during evaluation of this submission and changes to the Clinical Trial and Precautions sections relating to dyslipidaemia/CV endpoints initiated by TGA subsequent to main ACCORD Study.

### **Proposed conditions of registration**

The ACPM endorsed the conditions of registration proposed by the Delegate and specifically advised on the inclusion of the following:

- The satisfactory negotiation of the RMP most recently approved by the TGA.
- Finalisation of the PI and the CMI to the satisfaction of the TGA.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

## Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Lipidil containing fenofibrate for the new indication:

*Lipidil is indicated for the reduction in the progression of diabetic retinopathy in patients with Type 2 diabetes and existing diabetic retinopathy. Lipidil does not replace the appropriate control of blood pressure, blood glucose and blood lipids in reducing the progression of diabetic retinopathy.*

The **full indications** for the products are now:

*Lipidil is indicated as an adjunct to diet in the treatment of*

- *Hypercholesterolaemia;*
- *Types II,III, IV and V dyslipidaemia;*
- *dyslipidaemia associated with Type 2 diabetes.*

*Lipidil is indicated for the reduction in the progression of diabetic retinopathy in patients with Type 2 diabetes and existing diabetic retinopathy. Lipidil does not replace the appropriate control of blood glucose and blood lipids in reducing the progression of diabetic retinopathy.*

## Attachment 1: Product Information

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

## Attachment 2: Extract from the Clinical Evaluation Report

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## **Therapeutic Goods Administration**

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