EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assessment report

for

PRAVAFENIX

International nonproprietary name:

fenofibrate / pravastatin

Procedure No. EMEA/H/C/001243

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Laboratoires SMB S.A. submitted on 29 October 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Pravafenix, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 June 2008.

The applicant applied for the following indication:

"Pravafenix is indicated for the treatment of mixed dyslipidaemia (characterized by elevated levels of LDL-cholesterol and triglycerides) in high coronary heart disease risk patients.

The treatment is limited to patients who have not responded adequately to dietary measures and other non-pharmacological treatments (e.g. exercise, weight reduction) and to a treatment with pravastatin 40 mg monotherapy or an equivalent statin monotherapy regimen."

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC – fixed combination application

The application submitted is

composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P115/2009 on the granting of a product-specific waiver for the following condition:

Disorders of lipoprotein metabolism and other lipidemia

Information relating to Orphan Market Exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 15 November 2007. The Scientific Advice pertained to quality, clinical and nonclinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

Rapporteur: Pr. Lechat Co-Rapporteur: Dr. Calvo

- The application was received by the EMA on 29 October 2009.
- The procedure started on 18 November 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 5 and 11 February 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 5 February 2010.
- During the meeting on 15-18 March 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 18 March 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 August 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 and 5 October 2010.
- During the CHMP meeting on 18-21 October 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 11 November 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the CHMP consolidated List of Outstanding Issues on 29 November 2010.
- During the CHMP meeting on 13-16 December 2010, outstanding issues were addressed by the applicant in writing and in oral explanation. The second List of Outstanding Issues was adopted.
- Written responses to the second List of Outstanding Issues were submitted on 22 December 2010 and the final D195 joint assessment report was circulated on 14 January 2011.
- During the meeting on 17-20 January 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Pravafenix on 20 January 2011. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 17 January 2011.

2. Scientific discussion

2.1. Introduction

Mixed hyperlipidemia is characterised by an elevation of total cholesterol (TC) and triglycerides (TG), or by the elevation of low-density lipoprotein cholesterol (LDL-C) and TG, either acquired or familial. High-density lipoprotein cholesterol (HDL-C) level is often low.

Among the most notable elevated risk factors for the development of atherosclerotic cardiovascular (CV) disease are the elevated levels of LDL-C and the reduced levels of HDL-C.

Overall prevalence of mixed hyperlipidemia varies between 10 and 25% with many cases being the result of secondary causes. Familial mixed hyperlipidaemia is one of the most common hereditary disorders predisposing to early coronary death. Many patients have polygenic mixed hyperlipidemia and/or insulin resistance or diabetes mellitus, while a small fraction of patients (0.2%) have monogenic hyperlipidemia. Patients with polygenic or monogenic mixed hyperlipidemia form a high risk group for development of atherosclerosis especially coronary heart disease (CHD).

The achievement of lipid control in mixed dyslipidaemia usually requires progressive treatment: diet and exercise, followed by pharmacological intervention with an HMG CoA reductase (statins) in monotherapy, subsequently with statins in combination with niacin or fibrates.

Pravafenix 40/160 mg is a fixed dose combination (FDC) of pravastatin and fenofibrate formulated as hard capsules. Only one fixed dose combination containing 160 mg fenofibrate and 40 mg pravastatin is claimed.

Fenofibrate is a fibric acid derivative, introduced on the market in 1975. It exerts his effects mainly by activating the peroxisome proliferator-activated receptor-alpha (PPAR-alpha). It is generally authorised in patients with mixed dyslipidaemia. At the time being, the benefit/risk of fibrates is under review by the CHMP under article 31 of Directive 2001/83 EEC, as amended. Indeed, in 2005, due to the publication of the FIELD study (Effects of long term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus; a randomised controlled trial. Lancet 2005, 366, 9500: 1849-62; ERRATUM: Lancet, 2006, Vol 368, October 21, p1419-1420), a risk-benefit assessment on the fibrate class was performed, which concluded that overall, despite the long presence of fibrates on the market, there is only limited evidence of a long term clinical benefit from their use in the primary or secondary prevention of cardiovascular disease. It was agreed that the use of fibrates at first line therapy in the treatment of primary hypercholesterolaemia is not justified anymore. However, there are subgroups of patients, who may still benefit from this therapy. Thus, it was agreed that the product information for all fibrates should be updated to indicate that fibrates should be considered as first line treatment in patients with severe hypertriglyceridaemia with or without low HDL cholesterol. In patients with mixed hyperlipidaemia, fibrates should be given only when statins are contraindicated or not intolerated. Finally, a statement should be included in the Summary of Product Characteristics (SmPC) of all products to indicate that treatment with fibrates may reduce coronary heart disease events but no beneficial effect on all cause mortality in the primary or secondary prevention of cardiovascular disease has been confirmed. These recommendations were further challenged and a procedure under Art 31 of directive 2001/83 EEC, as amended was triggered.

Pravastatin sodium (hereinafter referred to as pravastatin) is a hydrophilic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin), which reduces cholesterol biosynthesis by interfering with the conversion of HMG-CoA to mevalonate, an early rate-limiting step in cholesterol biosynthesis. Pravastatin has been used worldwide for more than 10 years in the following indications:

Hypercholesterolemia: Treatment of primary hypercholesterolemia or mixed dyslipidaemia, as an adjunct to diet, when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate.

Primary prevention: Reduction of cardiovascular mortality and morbidity in patients with moderate or severe hypercholesterolemia and at high risk of a first cardiovascular event, as an adjunct to diet.

Secondary prevention: Reduction of cardiovascular mortality and morbidity in patients with a history of myocardial infarction or unstable angina pectoris and with either normal or increased cholesterol levels, as an adjunct to correction of other risk factors.

Post transplantation: Reduction of post transplantation hyperlipidaemia in patients receiving immunosuppressive therapy following solid organ transplantation.

2.2. Quality aspects

2.2.1. Introduction

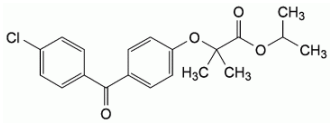
Pravafenix (Fenofibrate/Pravastatin sodium) 160/40 mg fixed dose combination is a new combination of two well known active substances described in the European Pharmacopeia. The proposed drug product is a hard gelatine capsule consisting of (A) a fatty semi-solid composition consisting of 160mg fenofibrate and (B) a coated tablet containing 40mg of pravastatin sodium.

Pravafenix *is packaged in HDPE* (High density polyethylene coloured white), *bottle* or *Aluminium/Aluminium blisters* (OPA – Alu – PVC)

2.2.2. Active Substance

Fenofibrate.

Fenofibrate is a white to off-white crystalline powder. It is insoluble in water (saturation solubility 0.8 µg/ml). As fenofibrate has no ionizable group, its water solubility is not influenced by the pH. Fenofibrate is a lipophilic molecule (log P is 4.6), and has the following structure:



Chemical names (IUPAC nomenclature): Isopropyl 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropionate

No polymorphism is known for fenofibrate. The melting point of fenofibrate is between 79°C and 82°C. Fenofibrate is a BCS class II molecule (low solubility, high absorption) and bioavailability is limited by dissolution from drug product.

Manufacture

The active substance is supplied by two manufacturers. For both of them a Certificate of Suitability (CEP) granted by the EDQM has been presented covering the manufacturing. Both manufacturers have declared the absence of use of material of human or animal origin in the manufacture of the substance.

Specification

Since the manufacturers have obtained a certification of suitability (CEP) granted by the EDQM, the information available is the one presented in the current edition of the PhEur. monograph for fenofibrate, including the additional tests for residual solvent (GC) mentioned in the corresponding CEPs.

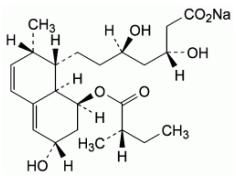
Batch analysis data from the manufacturers have been provided. All batches complied with the requirements from the active substance specification

Stability

The Certificate of Suitability provided by the manufacturers covers the re-test period and packaging material.

Pravastatin sodium.

Pravastatin sodium is a white or yellowish-white powder or crystalline powder. It is soluble in water (> 300mg/ml). Pravastatin Sodium exists in several polymorphic forms: A, B, C, D, E, F, G, H, H1, I, J, K and L which are not likely to induce different pharmacokinetic profiles or to influence the shelf life of the drug substance/drug products. This fact is explained by the high solubility of pravastatin in aqueous medium and by the water uptake of the powder which is independent on the polymorphic form. Pravastatin has the following structure:



Chemical names (IUPAC nomenclature): Sodium (3R,5R)-3,5-dihydroxy-7-[(1S,2S,6S,8S,8aR)-6-hydroxy-2-methyl-8-[[(2S)-2-methylbutanoyl]oxy]-1,2,6,7,8,8ahexahydronaphthalen-1-yl]heptone

Manufacture

Pravastatin is supplied by two different manufacturers. For both of them a Certificate of Suitability (CEP) granted by the EDQM has been presented covering the manufacturing processes. Both manufacturers have declared the absence of use of material of human or animal origin in the manufacture of the substance.

Specification

Since the manufacturers have obtained a certification of suitability of monographs of the European Pharmacopoeia, the information available is the one presented in the current edition of the PhEur. monograph for pravastatin sodium, including the additional tests for residual solvent (GC) mentioned in the corresponding CEPs. X-ray diffractograms reports are obtained for both suppliers and presented for information. No particle size specification is required for Pravastatin sodium. Nevertheless, particle size distribution and dissolution testing are assessed for information for the two proposed Pravastatin sodium suppliers, and found to be comparable on a routine basis.

Stability

The Certificate of Suitability provided by the two manufacturers covers the re-test period and packaging material.

Moreover, one of the manufacturer present stability studies for batches stored in long term conditions (2°C-8°C) and accelerated conditions (25°C/60%RH). Active substance batches were packed in the commercial container. Stability has been assessed for appearance, assay, water content and related substances level. A satisfactory re-test period has been defined for each supplier.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The medicinal product has been developed as a fixed dose combination of two well known molecules. The final form is a hard gelatin capsule consisting of (A) a fatty semi-solid composition consisting of 160mg fenofibrate and (B) a coated tablet containing 40mg of pravastatin sodium.

Since fenofibrate is a BCS class II molecule (low solubility, high absorption), the applicant has attempted to produce a pharmaceutical form of fenofibrate by increasing solubility using an amphiphilic excipient in order to enhance its bioavailability. The release of the active ingredient from the lipidic matrix occurs via an erosion-diffusion phenomenon when the composition comes into contact with gastro-intestinal fluids. The release does not occur through the melting of the composition since the melting range is between 45 and 50°C

The different excipients used were selected in order to allow complete dissolution of fenofibrate, enhance the dissolution rate and also reduces considerably the variability of the dissolution profiles. The excipients were also selected with a view to manufacturing feasibility.
The semi-solid formulation was optimized and several tests such as determination of the dissolved fraction in the drug product, characterization of the formulation by environmental scanning electron microscopy (ESEM) and differential scanning calorimetry (DSC) were also developed in order to adequately characterize the final fenofibrate semi-solid formulation.

Manufacturing holding time between the manufacture steps was defined and overall the process has been optimised based on previous experience in semisolid formulation.

Another main goal during development was to stabilize pravastatin within the drug product matrix, to prevent any interaction between the fatty mass containing fenofibrate and pravastatin. In order to achieve this, pravastatin was formulated in a separate tablet for filling into the capsule. Degradation of pravastatin is induced by acidic media and is accelerated by oxidants. To improve pravastatin stability, an alkaline agent and an antioxidant were introduced in the tablet formulation. As the tablet has to fall freely in the capsule, uncoated concave tablets were selected. Coating of the tablet was found necessary to give sufficient hardness to the tablet for subsequent handling and encapsulation, to prevent the formation of dust in the feeding hopper, to make the tablet slippery and to avoid direct contact between pravastatin and the fenofibrate hot blend.

Test of in vitro release rate of the combination fenofibrate and pravastatin were performed. The goal was to use the same dissolution medium to assess the release of fenofibrate and pravastatin. Conditions were optimized so as to be suitable for both drug substances. The aim of the dissolution test was mainly to assess the batch-to-batch consistency and the stability of the pharmaceutical product. The influence of different parameters such as pH or adding of different tensioactives were also studied.

Adventitious agents

BSE/TSE statements are provided for lactose monohydrate and for magnesium stearate (vegetable origin).
The gelatin capsules are from animal origin, valid CEP TSE certificates have been provided.

Manufacture of the product

The manufacturing process is satisfactorily described. The test proposed for IPC, frequency, sampling and specification are satisfactory. A flow-chart of the process including in-process control and validation test has been submitted.

The production process is performed in compliance with the principle of Good Manufacturing Practices, as laid down in volume IV of the rules Governing Medicinal Products in the European Community.

The preparation is performed in 3 main steps: Manufacturing of pravastatin coated tablet, manufacturing of fenofibrate semi-solid mass and filling of the hard gelatin capsules with coated tablet and fenofibrate semi-solid mass.

Product Specification

The release and shelf-life specifications of the finished product contains tests with suitable limits for appearance (visually),average of mass content (shel life), uniformity of dosage units (PhEur.), uniformity of the mass of the content (PhEur.), identification of drug substances (UV, HPLC), identification of ascorbyl palmitate(UV, HPLC), assay of drug substances, assay of ascorbyl palmitate, related substances, dissolution, identification of coloring agents and microbiological contamination(PhEur.- non routinely).

Descriptions and validation are given for the all the non compendial methods. The specifications, acceptance criteria and test methods are justified, a rational is provided in particular for degradation products. Limits for each individual degradation product are within the ICH identification and qualification thresholds at release and for shelf-life.

Stability *of the product*

Stability studies have been performed on 5 batches: 3 pilot scale batches manufactured and packaged in Aluminium/aluminium blister and 2 industrial scale batches manufactured and packaged in Aluminium/aluminium blister, in 60ml HDPE battle and in 150ml HDPE bottle. All batches were manufactured with fenofibrate and pravastatin sodium from two specific manufacturers.

All batches were placed on stability in ICH long term 25°C/60%RH, intermediate 30°C/65%HR and accelerated (40°C/75%RH) conditions.

All tested parameters remain within the specification for the period tested.

Based on the stability results submitted for up to 30 months for pilot batches in alu/alu blisters and 6 months for industrial batches in alu/alu blisters and HDPE bottles, the shelf-life as defined in the SmPC in the original packaging and the proposed storage conditions are justified.

2.2.4. Discussion and conclusion on chemical, pharmaceutical and biological aspects

It is unusual to have an encapsulated tablet; however, this is necessary to solve the stability problems of two separate active substances. The active substances and medicinal product have been adequately described. Excipients used in the formulation of the medicinal product and the manufacturing process selected are typical for capsules formulations. The results of the tests indicate that the active substances and the medicinal product can be reproducibly manufactured and therefore the product should have a satisfactory and uniform performance.

At the time of the CHMP opinion, there were minor unresolved quality issues, which have no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve it as a Follow-up Measures after the opinion, within an agreed time-frame.

2.3. Non-clinical aspects

2.3.1. Introduction

Pravafenix is a fixed-dose combination of the 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin), pravastatin, and of the fibric acid derivative (fibrate), fenofibrate, intended for use in the treatment of mixed hyperlipidemia. The non-clinical development programme is aimed to support the use of fenofibrate/pravastatin at the dose 160/40 mg.

Pravastatin was registered in the EU via individual national procedures. A referral procedure (Art. 30 of Council Directive 2001/83/EC) led to a harmonised labelling (European Commission Decision, 2 March 2004).

Fenofibrate has been marketed in Europe since the mid 1970's. It has been registered *via* individual national procedures at various strengths and dosing regimen.

The following guidelines have been used to assess the non-clinical development programme:
- Non-Clinical Development of Fixed Combinations of Medicinal Products (CHMP/SWP/258498/05)
- Repeated dose toxicity (CPMP/SWP/1042/99, Oct 2000).
- Duration of chronic toxicity testing in animals (rodent and non-rodent toxicity testing) (ICHS4A) (CPMP/ICH/300/95, May 1999)
- Toxicokinetics: the assessment of systemic exposure in toxicity studies (ICH S3A) (CPMP/ICH/384/95, Jun 1995)
- Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals intended for Human use (ICH S 2 (R1)) (CHMP/ICH/126642/08)
- Genotoxicity: a standard battery for genotoxicity testing of pharmaceuticals (ICHS2B) (CPMP/ICH/174/95, Mar 1998)
- Carcinogenicity: testing for carcinogenicity of pharmaceuticals (ICH SIB) (CPMP/ICH/299/95, Mar 1998)
- Need for carcinogenicity studies of pharmaceuticals (ICH SIA) (CPMP/ICH/140/95, Jul 1996)
- Dose selection for carcinogenicity studies of pharmaceuticals (ICH S1 C (R2)) (CPMP/ICH/383/95, Oct 2008)
- Reproductive toxicology: Detection of toxicity to reproduction for medicinal products including toxicity to male fertility (ICH S5A) (CPMP/ICH/386/95, Sep 1993)
- Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling (EMEA/CHMP/203927/05, Jan 2009)
- Environmental Risk Assessment of Medicinal Products for Human Use (CPMP/SWP/4447/00, Dec 2006)

2.3.2. Pharmacology

Primary pharmacodynamic studies

Pravastatin is a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor, commonly used in the management of hypercholesterolemia. HMG-CoA reductase catalyses the conversion of HMG-CoA to mevalonate. Competitive inhibition of HMG-CoA reductase in the liver by pravastatin leads to transcriptional up regulated production of the cell surface LDL receptor as well as decreased cholesterol synthesis. The associated reduction in intracellular cholesterol concentration induces LDL-receptor expression on the hepatocyte cell surface, which results in increased extraction of LDL-C from the blood and decreased circulating LDL-C concentrations. Pravastatin is a hydrophilic statin and is taken up by hepatocytes via a carrier-mediated active transport mechanism utilising the anion transport system.

Fenofibrate is a member of the fibrate class of lipid-lowering drugs. Its mechanism of action derives from activation of peroxisome proliferator-activated receptors α (PPRARα) that are expressed in the liver. The fenofibric acid, the active metabolite of the fenofibrate, is responsible for the primary pharmacodynamics effects of the drug: reductions in total plasma cholesterol, low-density lipoprotein cholesterol, triglycerides, and very low-density lipoprotein concentrations and increases in high-density lipoprotein cholesterol and apolipoproteins Apo AI and Apo AII concentrations. These effects are mediated by activation of PPARα. Fenofibrate also reduces the susceptibility of Very Low Density Lipoproteins (VLDL) and LDL to oxidative modification.

The pharmacodynamics profile of both pravastatin and fenofibrate is well known and the extent and scope of the bibliographic documentation provided in this application are considered appropriate. No new primary pharmacodynamic studies have been performed and this is considered acceptable.

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies on fenofibrate, pravastatin and the fixed dose combination have been conducted. Literature review characterising secondary pharmacology of fenofibrate and pravastatin in humans and animals has been submitted and this is considered appropriate since the secondary pharmacodynamics properties of fenofibrate and pravastatin are considered well known.

Clinical trials with pravastatin have shown positive impact of statins on cardiovascular morbidity and mortality due to its antithrombotic, anti-inflammatory properties and improvement in endothelial dysfunction. Pravastatin also seems to prevent the development of obesity and diabetes in diet-induced obese mice by increasing oxygen consumption and decreasing the respiratory quotient and has chemopreventive and neuroprotective effects. Fenofibrate can improve endothelial function, and protect blood vessels from alterations associated with metabolic disorders through its anti-oxidative,

anti-inflammatory and anti-thrombotic effects, and delays the onset of myocardial dysfunction in the model of pacing-induced heart failure in pigs.

Safety pharmacology programme

No safety pharmacodynamics studies on fenofibrate, pravastatin and the fixed combination of fenofibrate and pravastatin have been conducted. Literature references are provided and since there are no safety pharmacology related concerns regarding the use of these compounds, this is considered acceptable.

Pravastatin increases ALT and AST levels in humans but normally, these return to the baseline values without the need for treatment discontinuation and are not associated with hepatic symptoms. The most serious adverse effect associated with statin therapy is myopathy, which may progress to fatal or nonfatal rhabdomyolysis, myopathy and severe muscle problems. Pravastatin is less myotoxic than other statins due to the hydrophilic character of pravastatin and its selective affinity for liver cell *via* sodium-independent bile acid transporter. Fenofibrate and fenofibric acid influence nervous, respiratory, circulatory, digestive, urinogenital and other systems. However, these influences were caused by doses and concentrations much higher than those used in the treatment of hyperlipidaemia.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been performed. Due to the known clinical experience with fenofibrate and pravastatin, new pharmacodynamic interactions studies were not considered necessary by the CHMP.

2.3.3. Pharmacokinetics

The pharmacokinetic properties of fenofibrate and pravastatin are considered well-known following different routes of administration in a number of species. No absorption, distribution, metabolism and pharmacokinetic studies have been performed, but bibliographical references have been provided to address the pharmacokinetics patterns of fenofibrate and pravastatin.

Absorption
Pravastatin is well absorbed from the gastrointestinal tract of rats, dogs and monkeys. A study on bile duct cannulated rats showed that pravastatin is almost equally absorbed through a wide area from the stomach to the ileum. The extent of absorption of pravastatin is estimated to be approximately 65% in rats based on biliary excretion and 45% in dogs based on urinary excretion. A high bioavailability was observed in all species except monkeys, where it was only 18%. The drug is absorbed from the upper part of the small intestine, probably *via* the proton-coupled carrier-mediated transport.

After absorption, fenofibrate is rapidly hydrolysed into its major metabolite, fenofibric acid. The reduction of the carbonyl group of fenofibric acid results in another active but minor metabolite, the reduced fenofibric acid. A significant proportion of fenofibrate is, however, not completely absorbed by the gastrointestinal tract, as suggested by the considerable amounts of intact fenofibrate found in the faeces.

Distribution
After oral administration of 500mg/kg pravastatin to rats, the time to attain the maximum plasma concentration is around 1 hour, and the maximum level is about 1 μg/ml. The plasma protein binding of the drug is almost the same in rats and human, i.e. 43% to 60%, which is significantly lower than that of other statins. Pravastatin is distributed mostly into the liver and the gastrointestinal tract after both intravenous and oral dosing in rats and oral dosing in dogs. The concentration in other tissues was close to, or less than that in plasma. Pravastatin is subjected to a first-pass. The first-pass removal rate is about 0.7. A nonlinear relationship was observed between the liver and plasma concentrations. These results suggest that the dose dependency in the distribution volume of pravastatin is due to a saturable uptake by the liver.

The tissue radioactivity concentration was measured in radio-labelled fenofibrate in specific intervals after single oral administration to Sprague-Dawley rats. The highest concentration at 30 minutes after administration was found in the liver, the kidney and the stomach corresponding to 2 to 3 times the plasma concentration. The protein binding rate of plasma concentration was about 99% for both male and female rats.

Metabolism
Pravastatin is not significantly metabolised by CYP3A4, but is largely excreted as parent compound into the faeces *via* the bile and into the urine. After single oral administration of radio-labelled pravastatin to rats and monkeys, unchanged pravastatin represented 47% and 60% of the total biliary radioactivity, respectively, with small recoveries of metabolites (less than 11%). The identified metabolites were 3'α-iso- and 6'-epi-pravastatin both formed by isomerisation, pravastatin lactone, 3',5'-dihydrodiol-pravastatin and pravastatin 4'a α-glutathione conjugate. In plasma, pravastatin accounted for only 5% and 11% of the total plasma radioactivity in rats and monkeys, respectively, although pravastatin is the major component (70%) in dog plasma. Unchanged pravastatin accounts for approximately 20-30% of the rat liver radioactivity.

After absorption, fenofibrate is rapidly and completely hydrolysed to its major metabolite, fenofibric acid. The reduction of the carbonyl group of fenofibric acid results in another active but minor metabolite, the reduced fenofibric acid. Both metabolites are conjugated with glucuronic acid and excreted mainly in urine. The major urinary metabolite is fenofibric acid ester glucuronide. Much smaller amounts of fenofibric acid and benzhydrol and his glucuronide are also found. Glucuronidation of fenofibric acid and reduced fenofibric acid is minor in rats and guinea pigs and is not detectable in dogs. In addition, unknown polar metabolites were detected in rats, dogs and guinea pigs but were not investigated further.

Neither fenofibrate nor fenofibric acid undergo oxidation via the cytochrome P450 pathway to any significant extend. *In vivo* studies using human liver microsomes indicate that fenofibrate and fenofibric acid do not inhibit cytochrome P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6 and mild to moderate inhibitors of CYP2C9 at therapeutic concentrations. Most of fenofibric acid is glucuronidated by the UDP-glucuronosyl transferases UGT1A9 and UGT2B7, which make fenofibric acid more hydrophilic and biologically inactive facilitating renal and biliary excretion.

Excretion
In dogs, the total recovery of the radioactive dose of pravastatine in urine and faeces collected over 96 hours averaged 90%. Recovery of the radioactive dose averaged 29% after intravenous injection, and 12% after oral injection. About 18% (after IV) and 6.5% of unchanged pravastatin was recovered from the urine between 0 and 48 hours. In monkeys, after oral dosing of radio-labelled pravastatin, most radioactivity is recovered in the faeces (84%) and 2% of the dose is excreted in the urine. In rats, after oral dosing of radio-labelled pravastatin, 83-87% of the radioactivity is recovered in the faeces, with less than 4% of the dose excreted in the urine. Pravastatin and its metabolites excreted in the bile undergo enterohepatic circulation in rats. The excretion of fenofibrate in rats was influenced by the dosage form given.

Pharmacokinetic drug interactions
Fenofibrate does not adversely influence the metabolism or pharmacokinetics of pravastatin and pharmacokinetic literature data on both fenofibrate and pravastatin as separate compounds or in association confirm a minimal and stable interaction between both compounds, since co-administration of fenofibrate has modest effects on pravastatin systemic exposure. Further assessment of the human pharmacokinetics with the drug combination is provided in the clinical assessment report.

2.3.4. Toxicology

Literature review characterising the pharmacokinetics of the separate compounds has been submitted. In addition, three new studies with the combination in rats have been conducted: an IV single dose study, an oral *28-day* study and an oral *13-week* study. This is in accordance with the Guideline on the non-clinical development of fixed combination of medicinal products (EMEA/CHMP/SWP/258498/2005).

Single dose toxicity
A single dose toxicity study has been conducted in rats with the fixed dose combination of fenofibrate and pravastatin administered by an intravenous route. This study has been performed according to GLP requirements to provide data on the acute toxicity of combination product in rats after a single intravenous injection. The description of the study is given in the table below.

Summary of acute toxicity study with fixed dose combination, fenofibrate and pravastatin

Study ID	Species/ Sex/Number/ Group	Dose (g/kg bw) /Route	Observed Maximum Non-Lethal Dose (mg/kg)	Major findings
TNO - V5245/01	Rat/both/4 per sex and 106/30 mg/kg dose and 3 male per 212/60 mg/kg	106/30 /i.v. 212/60 /i.v.	> 106/30 Fenofibrate and Pravastatin	death of 2 out of 3 males, haemorrhages in the lungs, black tail in 1 male, blue discoloured tail in 3 male

The results indicated that a mixture of 106 mg fenofibric acid and 30 mg pravastatin/kg bodyweight is the maximum tolerated dose in Wistar rats for which no mortality and major toxicity occurred after intravenously administration. The non observed effect level (NOEL) has not been determined, since 3 of the 4 males in 106/30 mg/kg fenofibrate and pravastatin group showed tail discolourations. Mortality was observed at the dose of 212 mg/kg of fenofibric acid and 60 mg/kg of pravastatin. The maximum non-lethal dose is 106/30 mg/kg.

Repeat dose toxicity

No repeat-dose toxicity studies in pravastatin and in fenofibrate separately have been submitted within this dossier, since information about their acute toxicity has been published in the literature. However, two repeat-dose studies with the fixed dose combination of fenofibrate and pravastatin, studies TNO-V5245/02 and TNO–P8003, have been performed. Both were performed in Wistar rats, with the duration of 28 days and 13 weeks. A summary of repeated-dose oral studies is tabulated below.

Overview of repeat-dose toxicity studies performed with fixed dose combination of fenofibrate and pravastatin.

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
TNO-V5245/02	Wistar rats /both /5 by sex and dose level	0/0, 6/1.67, 40/10 and 240/60 mg/kg bodyweight / Oral gavage doses	28 days	6/1.67 mg/kg b.w./day	Severe, bilateral hydronephrosis in a female in 12/3 mg/kg Fenofibrate/Pravastatin group, no treatment-related events
TNO-P8003	Wistar rats /both /10 by sex and dose level	0/0, 2.4/0.6, 7.2/1.8 and 12/3 mg/kg bodyweight/day /Oral gavage doses	13 weeks	2.4/0.6 mg/kg b.w./day	No major findings

In the *28-day study*, liver was shown to be the target organ. Centrilobular hypertrophy occurred at 40/10 mg/kg of fenofibrate/pravastatin and at higher doses; at 240/60 mg/kg was detected increased ASAT in females only and increased ALP in both sexes. Muscular effects were observed at 40/10 mg/kg and higher doses, which was consisted with mononuclear cell infiltrate in the skeletal muscle and myositis.

In the *13-week study*, liver was also the target organ. Centrilobular hypertrophy was noted at 7.2/1.8 mg/kg of fenofibrate/pravastatin and higher doses and increased ALP in males at 12/3 mg/kg of fenofibrate/pravastatin. Effects on pancreas (chronic inflammation and focal pancreatitis) were observed in all dose groups but no statistical difference from controls was achieved. It should be noted that higher glucose levels were observed in the 28-day study but not found in the 13-week study. Submitted toxicity studies with fenofibrate or pravastatin alone did not reveal such effects but pancreatitis is mentioned as an adverse effect for both active substances in the respective SmPCs. Therefore, the relation of pancreatic effects with the treatment cannot be excluded. No increase in CK values was reported and no effects on muscles were observed. The safety margin at the NOAEL is <1

based on AUC or C_{max} for fenofibrate, but cannot be calculated for pravastatin because plasma concentrations were below the limit of quantification.

Initially, the CHMP questioned the selection of the dose in the 13-week study, since this was based on human dose and not on human exposure. As a consequence, tested animals might not have been significantly exposed, preventing a relevant assessment of the toxicity of this new combination, in particular view of the new effects or effects resulting from potentiation and their reversibility. The doses tested in the 13-week study could have been too low based on the 28-day study where no toxicity concern appeared. However, since clinicians considered that no concern regarding exposure or interaction between both components arises in humans, this issue was solved.

The CHMP also noted the findings of this study with respect to the pancreatic, muscular, renal and hepatic effects, taking into account their relevance for humans and all available clinical data. Therefore, appropriate information has been captured in the SmPC of Pravafenix: warning regarding pancreatitis, contraindication to severe renal impairment, need of monitoring of myopathy, and other.

Genotoxicity
No new studies have been performed, which is acceptable according to the current guideline: The Non-Clinical Development of Fixed Combinations of Medicinal Products (EMEA/CHMP/SWP/258498/2005). There is no concern with regard to genotoxic potential of fenofibrate and pravastatin in this fixed combination based on the provided literature references regarding genotoxicity potential for fenofibrate and pravastatin separately.

Carcinogenicity
Specific studies have not been conducted, which is acceptable according to the guideline: Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products (EMEA/CHMP/SWP/258498/2005). There is no concern regarding carcinogenicity potential of fenofibrate and pravastatin in humans in this fixed combination.

Reproduction Toxicity
The absence of new reproductive and developmental toxicity studies is acceptable to the CHMP considering the well known profile of fenofibrate and pravastatin. Overview of reproduction studies published in the literature has been submitted. Pravastatin did not induce adverse effects on reproduction. Fenofibrate was embryotoxic (skeletal variations, reduced ossification) at materno-toxic doses. Neonatal deaths were also observed at materno-toxic doses. The SmPC of the fenofibrate-containing products states that prolongation of the gestation period and difficulties during delivery were observed at high doses. Adequate information on these effects was also included in the SmPC of Pravafenix. Pravastatin is contraindicated during the pregnancy and thus, the use of Pravafenix during pregnancy is also contraindicated. This information is stated in the SmPC.

Toxicokinetic data
Toxicokinetic measurements were provided as part of the repeat dose toxicity studies and only at the high dose where adverse effects were observed. Therefore, no safety margin between animal exposure at the NOAEL and human exposure can be calculated.

Local Tolerance
Based on the literature review, no specific concerns for the local tolerance for either fenofibrate or pravastatin can be identified. During the newly submitted repeat-dose toxicity studies performed with the combination, examination of the digestive tract did not reveal any particularity.

Other toxicity studies
No other specific toxicity studies have been performed. The submitted literature data on immunogenicity, antigenicity and excipients raised no concern.

2.3.5. Ecotoxicity/environmental risk assessment

The environmental risk assessment (ERA) is based on data from bibliographic references on fenofibrate and pravastatin. The CHMP raised several concerns regarding the submitted data and considered the ERA as not yet acceptable. Determination of the partition coefficient octanol/water for any of the active

substances, the Predicted No Effect Concentration (PNEC) calculation and lower values of assessment factors should be re-assessed.

The results from the additional studies were not considered required by the Committee before the adoption of the positive CHMP opinion and it is confirmed that these applications comply with Article 6 of Regulation 726/2004 having regard to the requirements of Article 8(3) (ca) of Directive 2001/83. Therefore, a specific post-authorisation follow up measure has been agreed to perform an environmental risk assessment fully in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00). The regards amongst others determination of the adsorption/desorption behaviour of the substances, determination of bioaccumulation, determination of the ready biodegradability, determination of the long-term fish toxicity, and other tests.

2.3.6. Discussion on non-clinical aspects

Bibliographical references have been provided to address the nonclinical pharmacodynamics and pharmacokinetics pattern of fenofibrate and pravastatin. Both, the pharmacodynamic and pharmacokinetic profile of these drugs are well known and the extent and scope of the bibliographic documentation provided are considered appropriate. No new pharmacodynamic, safety pharmacology or pharmacokinetic studies have been performed and this is considered acceptable. No new studies have been performed on genotoxicity, carcinogenicity, reproductive and development toxicity, antigenicity, immunotoxicity, dependence, metabolites and impurities toxicity, which is acceptable according to the Guideline on The Non-Clinical Development of Fixed Combinations of Medicinal Products (EMEA/CHMP/SWP/258498/2005). There are no concerns regarding local tolerance, antigenicity, immunotoxicity, dependence and impurities of the combination of fenofibrate and pravastatin.

The following toxicological studies focusing on the examination of toxicity of fenofibrate and pravastatin combination have been conducted: single-dose intravenous toxicity study with Fenofibric acid and Pravastatin in rats (TNO-V5245/01), 28 days repeat-dose oral toxicity study with fenofibrate and pravastatin in rats (TNO-V5245/02) and repeat-dose oral gavage sub-chronic toxicity study with a fixed combination of a mixture of fenofibrate and pravastatin in rats, including a 4-weeks recovery period (TNO-8003). The toxicity effects observed in animals have been adequately reflected in the SmPC of the fixed dose combination.

Regarding the ecotoxicity and environmental risk issues, this assessment is based on data from bibliographic references on fenofibrate and pravastatin. The CHMP requested the conduct of an additional Phase II environmental fate and effect analysis during the post-authorisation phase.

2.3.7. Conclusion on the non-clinical aspects

The non clinical programme for Pravafenix is considered appropriate to support the marketing authorisation application for Pravafenix, including the conduct of three toxicity studies. The submitted environmental risk assessment is not fully acceptable and a new ERA programme will be conducted as agreed in form of a specific follow up measure.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for the marketing authorisation of the fixed dose combination medicinal product fenofibrate/pravastatin in the frame of the centralised procedure according to Regulation (EC) No 726/2004. The application is submitted in accordance with Article 3(2)a of the above mentioned regulation and with Article 10(b) of the Directive 2001/83/EC.

For the assessment of the clinical properties of Pravafenix, a lipid lowering agents, both the Note for Guidance (NfG) on fixed medicinal products (CPMP/EWP/240/95) and the Note for Guidance on clinical investigation of Medicinal Products in the treatment of Lipid disorders (CPMP/EWP/3020/03), apply. In

line with the NfG on fixed dose combination medicinal products (CPMP/EWP/240/95), the proposed clinical development was performed according to the requested indication. The FDC is proposed to be indicated as second line therapy, when monotherapy with each component has not demonstrated beneficial effects on lipid parameters.

Formal scientific advice concerning quality, preclinical and clinical development on the development of Pravafenix was requested from the CHMP in August 2007. An oral explanation was held in front of the Scientific Advice Working group on October 2007. Questions on clinical development were mainly related to the mechanism of action of both active substances, the pharmacokinetic and efficacy studies to be performed for the development of a fixed dose combination (including food effect and specific population such as elderly, and patients with hepatic and renal failure). The CHMP recommendations have been only partially followed.

In summary, the conducted clinical development programme for Pravafenix focused on the examination of the pharmacokinetic and biopharmaceutical properties of the combination (eight clinical studies) as well as on the evaluation of it efficacy and safety (four clinical studies). The overall tabulated summary of the clinical studies is presented below. Results of these studies were supported by the bibliographic data for the individual compounds.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The following biopharmaceutical studies were performed during the development phase of the new fixed dose combination of fenofibrate 160 mg and pravastatin 40 mg:

Overview of the pharmacokinetic and biopharmaceutical studies

SMB-FENO-SD012	Comparative study of the bioavailability of fenofibric acid after single oral dose of two formulations of fenofibrate in 18 healthy subjects: FENOGAL® 160 versus LIPIDIL-TER® 160, single dose, 2-way, cross-over study.
SMB-FEPRA-SD081	Comparative study of the bioavailability of Fenofibrate and Pravastatin after single oral doses of the combination Fenofibrate-Pravastatin 160-40 mg versus the coadministration of the marketed form of pravastatin 40 mg and the marketed form of fenofibrate 160 mg in fed condition in 36 healthy subjects: open, randomised, single dose, 2-way, 19 days, cross-over study
SMB-FEPRA-SD082	Comparative study of the bioavailability of pravastatin after single oral dose of the combination of Fenofibrate-Pravastatin 160-40 mg in fed conditions versus ELISOR 40 mg in fed and in fast conditions , in 36 healthy subjects: Open, randomised, single dose, 3-way, cross-over study
SMB-FEPRA-SD083	Comparative study of the bioavailability of Fenofibrate and Pravastatin after single oral dose of two different formulations of the combination Fenofibrate-Pravastatin 160/40 mg in fed conditions in 36 healthy subjects: Open, single dose, randomised, 2-way, 19 days cross-over study
SMB-FEPRA-SD084	Comparative study of the bioavailability of Fenofibrate and Pravastatin after single oral doses of the combination Fenofibrate-Pravastatin 160-40 mg in fed and fasting conditions in 36 healthy subjects: open, single dose, randomised, 2-way, 19 days, cross-over study
SMB-FENOPRAVA-SS031	Comparative study of the bioavailability after multiple oral dose of the combination of Fenofibrate-Pravastatin 160-40 mg versus LIPANTHYL®160 mg versus PRAVASINE®40 mg in fed conditions in 36 healthy subjects: Randomised, multiple dose, 3-way, cross-over study
SMB-FEPRA-SS071	Comparative study of the bioavailability of Fenofibrate and Pravastatin after multiple oral doses of the combination Fenofibrate-Pravastatin 160-40 mg versus the coadministration of the marketed form of pravastatin 40 mg and the marketed form of fenofibrate 160 mg in fed condition in 36 healthy subjects: open, randomised, multiple doses, 2-way, 33 days cross-over study
SMB-FEPRA-SS072	Comparative study of the bioavailability of Fenofibrate and Pravastatin after multiple oral doses of the combination Fenofibrate-Pravastatin 160-40 mg versus the coadministration of the marketed form of pravastatin 40 mg and the marketed form of fenofibrate 160 mg in fasting condition in 36 healthy subjects:Open, randomised, multiple doses, 2 way, 33 days, cross-over study

The Phase III clinical development programme in support of the claimed indication in patients with mixed hyperlipidaemia included 4 main studies (see table below), of which two pivotal studies performed in Europe:
- SMB-FEBRA-0303, performed in patients with mixed hyperlipidaemia and high cardiovascular risk;
- FENOPRA-III-06-01 performed in type 2 diabetic patients with mixed hyperlipidaemia.
One confirmatory study was performed in the United States: Sc-PRAVA-06-02. The fourth study performed in Europe (FENOPRA-III-05-1) was mainly a 24-week open-label safety study. All phase III controlled efficacy study were performed using the final formulation.

Study No.	Study objective, population	Randomised patients	Duration	Dosage	Primary efficacy
SMB-FEPRA-0303 (EU)	Efficacy/safety in high risk patients with mixed hyperlipidaemia (NCEP ATP III)	248	Controlled double-blinded efficacy phase: 12 weeks Safety open-label period: 52 weeks	Feno/Prava 160/40mg (N=120) Pravastatin 40mg (N=119)	Percent change in Non HDL-C
FENOPRA-III-06-1 (EU-Diabetes)	Efficacy/safety in T2DM patients with mixed dysmipidaemia: - without CVD (stratum 1), or - with CVD (stratum 2)	564	Controlled double-blinded efficacy phase: 12 weeks Safety open-label period: 52 weeks	Stratum 1: -Feno/Prava160/40mg (N= 145) - Simvastatin 20mg (N=146) Stratum 2: - Feno/Prava160/40mg + ezetimibe 10 mg (N= 133); - Simvastatin 20mg + ezetimibe 10 mg (N=133)	Percent change in Non HDL-C
Sc-Prava-06-02 (USA)	Efficacy/safety in patients with mixed hyperlipidaemia	481	Controlled double-blinded efficacy phase: 12 weeks Safety open-label period: 52 weeks	Feno/Prava 160/40mg) (N=238) Pravastatin 40mg (N=111) Fenofibrate 160mg (N=119)	Percent change in Non HDL-C
FENOPRA-III-05-1 (EU) Safety study	Safety study in patients with mixed hyperlipidaemia	344	Open label	Not applicable	Safety endpoints

2.4.2. Pharmacokinetics

Information regarding pharmacokinetic properties of each single substance by the use of scientific bibliographic overview has been provided. This is considered acceptable because the individual pharmacokinetic profiles of fenofibrate and pravastatin are well established.

Several biopharmaceutical studies were performed with the new fixed dose combination of fenofibrate 160 mg and pravastatin 40 mg (SMB-FENO-SD012, SMB-FEPRA-SD081, SMB-FEPRA-SD082, SMB-FEPRA-SD083, SMB-FEPRA-SD084, SMB-FENOPRAVA-SS031, SMB-FEPRA-SS071, SMB-FEPRA-SS072). Six biopharmaceutical studies were conducted in order to compare the new fixed dose combination with the single product or the co-administration of the two reference drug products. Those comparisons were performed at a single dose or at multiple doses and in fasting or fed state. The used dosage is 160 mg of fenofibrate compared to 160 mg fenofibrate of marketed form (LIPANTHYL 160 mg or LIPIDIL-TER 160 mg available on the EU market) and 40 mg pravastatin compared to 40 mg pravastatin of marketed form (PRAVASINE PROTECT, ELISOR or PRAVASINE 40 mg available on the EU market). Investigation of the potential for drug-drug interaction of the active components of Pravafenix was also conducted. Two additional bioavailability studies were also submitted for the following reasons:
- SMB-FENO-SD012: The MA for a formulation of Fenofibrate 160 mg (FENOSUP, FENOGAL, CIL 160 mg - a product essentially similar to LIPANTHYL SUPRA/LIPIDIL-TER 160 mg) has been obtained in different European countries. As the composition of the former fenofibrate formulation is quite similar

to the composition of the fenofibrate 160 mg used in the fixed combination, this bioequivalence study is submitted as supportive in the present application.
- SMB-FEPRA-SD083: A partner company performed a pharmaceutical and clinical development of the 160/40 mg fenofibrate/pravastatin formulation in the USA. In order to bridge the clinical data between the EU and the US formulation, a bioequivalence study between the two formulations has been performed.

From the review of the submitted results of these clinical trials, the CHMP concluded the following:
- Conflicting results were obtained regarding the bioequivalence (BE) of the fixed combination and the free co-administration of Lipanthyl 160 mg and Pravasine 40 mg. The pivotal single-dose study (SMB-FEPRA-SS 081), conducted under fed conditions showed BE of Pravafenix and the free co-administration of Lipanthyl and Pravasine. However, findings of study SMB-FEPRA-SS 081 were not confirmed by the repeated-dose study SMB-FEPRA-SS 071, also performed under fed conditions. Indeed, this study failed to demonstrate BE with regard to fenofibrate. Lower systemic exposure to fenofibrate (approximately 20 %) was observed. Study SMB-FEPRA-SS 0072 performed at steady-state and under fasting conditions showed noticeable differences between the biopharmaceutical performances of the fixed combination drug product (FDC) and the co-administration of Pravasine and Lipanthyl. Lower bioavailability is observed with the FDC. The bioavailability of fenofibrate and pravastatin is decreased by approximately 50% and 20 %, respectively. Therefore, the CHMP raised a major objection and requested a thorough discussion on the impact of these findings on the efficacy/safety of Pravafenix in patients switched from the free co-administration of Pravasine 40 mg and Lipanthyl 160 mg to Pravafenix.
- The US Pravafenix formulation investigated in one phase III efficacy/safety clinical trial is demonstrated to be bioequivalent to the EU formulation.
- The bioavailability of both ingredients of Pravafenix is markedly influenced by food intake in a symmetrical way: Food intake noticeably enhances the bioavailability of fenofibrate. Higher AUC_t (by approximately +40 %) and C_{max} (approximately +300%) were observed under fed conditions. Conversely, systemic exposure to pravastatin is markedly decreased (by approximately -50%) by food intake. It is noteworthy, that such decrease in pravastatin bioavailability is also observed with Pravasine.
- The results of the examination of the potential for drug-drug interactions between pravastatin and fenofibrate are presented in a separate chapter.

In response, the impact of the decrease in systemic exposure to pravastatin was thoroughly discussed. It is agreed that the differences in systemic exposure observed under fed conditions would not noticeably impact the efficacy of the statin component. The much more pronounced difference in systemic exposure under fasting conditions for fenofibrate may plausibly impact the efficacy of the fibrate component of the FDC, however a clear statement has been introduced in the SmPC on the inter-changeability of the FDC and free co-administration of the monocomponent drug products. The information regarding the intake of the drug with food was also strengthened in the SmPC. Thus, the CHMP considered this issue could be considered resolved. From the initially performed investigations, it would appear that the FDC does not perform similarly as the freely co-administered monocomponent drug products (Pravasin 40 mg + Lipanthyl 160 mg). Under fasting conditions, the systemic exposure to fenofibrate when administered as Pravafenix is significantly lower than that observed with Lipanthyl (50% lower). Such difference could not be considered clinically irrelevant. Nevertheless, the warnings regarding the possibility to switch the FDC and the monocomponent drug products as well as the information regarding the food intake introduced in the updated SmPC could be considered an acceptable alternative to manage the differences in the biopharmaceutical performances mentioned above.

Absorption, Distribution, Elimination

A brief overview of the pharmacokinetic properties of pravastatine and fenofibrate is given below.

Hydrolysis of fenofibrate by tissue and plasma esterases to the active principal metabolite fenofibric acid appears to commence concomitantly with absorption. It was reported that unmodified fenofibrate was not detectable in the plasma of healthy volunteers. The C_{max} of fenofibric acid occurs within 6 to 8 hours after fenofibrate administration and the absorption of fenofibrate is increased when administered with food. Steady-state plasma concentrations of fenofibric acid are achieved after 5 days and the agent does not accumulate over time with repeated administration. The apparent volume of distribution of fenofibric acid was 0.89 L/kg in healthy subjects. Fenofibric acid is highly bound (>99%)

to plasma proteins. Serum protein binding (mainly to albumin) exceeds 99% and is concentration-independent over the therapeutic dose range. Mean terminal phase elimination half-life values ranging from 19.6 to 26.6 hours have been observed following administration of single doses of fenofibrate 300 mg to healthy volunteers. The mean elimination half-life observed after repeated administration of fenofibrate 300 mg daily was not significantly different from that seen after single. Fenofibrate is metabolised to a number of compounds in humans. The principal excretion pathway for the metabolites in humans is the urinary tract. Faecal excretion also occurs to a variable extent depending on the rate of absorption. Approximately 60% of a dose of radiolabelled fenofibrate appears in the urine, and 25% is excreted in the faeces.

Following the oral administration, pravastatin is rapidly absorbed, and the time (t_{max}) to attain the maximum drug serum concentration is around (1 hour). The absolute bioavailability averages 18% based on AUC and urinary excretion of intact pravastatin. This low systemic absolute bioavailability has been attributed to both, the incomplete absorption (34%) and the hepatic metabolism (first-pass effect with subsequent biliary excretion), when pravastatin is administered orally. Administration of pravastatin with food decreases the bioavailability of the drug by one-third. However, the food effect does not significantly affect the lipid-lowering activity of the drug. Further discussion on the effect of food on pravastatin is given below in a separate section. In healthy volunteers, the volume of distribution of pravastatin is 0.5L/kg at a steady state and 0.88 L/kg during the elimination phase. The level of protein binding of pravastatin is 43 to 54%. The binding to other cellular elements of blood is negligible. The systemic elimination rate constant of pravastatin is much higher than the absorption rate constant. Because of the rapid elimination, pravastatin does not accumulate in plasma after repeated administration. It is eliminated through both, the renal and non-renal routes, and 64% of an intravenous dose is excreted into the urine and faeces as intact drug. The systemic and renal clearances are 0.810 and 0.378 L/h/kg, respectively, so that renal and non-renal routes of elimination account for 47% and 53%, respectively.

Dose proportionality and time dependencies

This is a MAA for Pravafenix - one strength (160 mg fenofibrate / 40 mg pravastatin) and therefore no dose proportionality is to be evaluated.

Special populations

No pharmacokinetic data are provided in patients with renal insufficiency receiving the fixed combination or fenofibrate and pravastatin concomitantly. The SmPC for fenofibrate (Lipanthyl Micro 200) includes a specific reduction of dose depending on the rate of creatinine clearance. Taking into account the dose for fenofibrate in the FDC (160 mg) and the SmPC for fenofibrate, the Pravafenix SmPC includes a contraindication for moderate to severe renal impairment.

No new data or bibliographic review is provided regarding patients with hepatic impairment. Fenofibrate has not been studied in patients with hepatic impairment, but is contraindicated in patients with severe liver disease. Pravastatin increase its bioavailability in patients with hepatic disease. The SmPC for Pravafenix therefore recommends a contraindication in patients with severe hepatic impairment including biliary cirrhosis or active liver disease including unexplained persistent elevations in liver function tests. A special warning on management of patients with hepatobiliary disorders is also included. Please refer to the discussion on clinical efficacy.

Regarding gender, the SmPC for fenofibrate states that no pharmacokinetic difference between males and females has been observed for fenofibrate. With respect to pravastatin, new information related to SLCO1B1 polymorphism and gender has been published recently, but the impact of these findings needs further investigations. The influence of race on the pharmacokinetics of fenofibrate has not been studied, however; fenofibrate is not metabolised by enzymes known for exhibiting inter-ethnic variability. European-Americans had significantly higher plasma pravastatin AUC and C_{max} values than African-Americans even when adjusted for the presence of the SLCO1B1 521C or 388G variant allele. However, this difference did not suggest clinically relevant differences based on ethnicity. Therefore, there would not appear to be a requirement to add any particular advice in the Pravafenix SmPC. Weight is not expected to have a clinically significant influence on the pharmacokinetic behaviour of the FDC.

Concerning the elderly, no specific investigations have been performed in this sub-group for the FDC. Recommendations regarding the use of the fixed combination are inferred from experience with the use of each component separately in the elderly patients. Pravafenix pharmacokinetics has not been evaluated in children or adolescents.

Pharmacokinetic interaction studies

Fenofibrate has a low potential for drug-drug interaction since it does not undergo a significant oxidation metabolism by CYP 450 isoenzymes. Pravastatin metabolism is not mediated by the CYP450. Therefore, drug-drug interaction potential of the active ingredients of the FDC under review appears to be limited. Nevertheless, formal testing for such interaction is required. A three- arm cross-over study at steady state under fed conditions, study SMB-FENOPRA-SS31, was performed for this purpose. This was a comparative study on the bioavailability of fenofibrate and pravastatin after multiple oral doses of one formulation of fenofibrate/pravastatin 160/40 mg, one formulation of fenofibrate 160 mg and one formulation of pravastatin 40 mg in 36 healthy subjects. In total, 37 subjects were randomised and 34 completed the study.

The main pharmacokinetic findings for the study are summarized in the tables and figures below.

Pharmacokinetic results and statistical analysis of comparative study for **Fenofibric acid** (log-transformed data)				
Parameters	LIPANTHYL ® 160 mg	Fenofibrate-Pravastatin 160-40 mg	Bioequivalence 90 %CI	Point estimate
AUC_{∞} (µg.h/ml)	278.97 ± 131.69	263.36 ± 114.98	[85.71 ; 100.69]	92.90
AUC_{τ} (µg.h/ml)	90.31 ± 32.34	81.05 ± 29.04	[82.47 ; 94.81]	88.43
C_{max} (µg/ml)	10.45 ± 3.56	9.48 ± 3.24	[83.33 ; 96.43]	89.64
C_{min} (µg/ml)	3.03 ± 1.39	2.74 ± 1.29	[83.65 ; 97.42]	90.27
t_{max} (h)	3.91 ± 1.06	4.60 ± 1.17	NS	-
F (%)	202.21 ± 38.65	203.79 ± 46.01	[92.91 ; 106.58]	99.51
$t_{1/2}$ (h)	17.67 ± 4.29	18.33± 4.27	[97.76 ; 110.11]	103.75

Pharmacokinetic results and statistical analysis of comparative study for **Pravastatin** (log-transformed data)				
Parameters	PRAVASINE ® 40 mg	Fenofibrate-Pravastatin 160-40mg	Bioequivalence 90 %CI	Point estimate
AUC_{∞} (ng.h/ml)	88.21 ± 51.44	111.74 ± 92.81	[103.21 ; 134.68]	117.90
AUC_{τ} (ng.h/ml)	80.68 ± 44.60	96.64 ± 63.54	[102.27 ; 132.11]	116.24
C_{max} (ng/ml)	30.55 ± 18.39	37.96 ± 27.92	[103.47 ; 137.68]	119.36
C_{min} (ng/ml)	0.51 ± 0.05	0.57 ± 0.23	[97.89 ; 114.26]	105.76
t_{max} (h)	1.71 ± 0.83	1.88 ± 0.43	NS	-
F (%)	884.68 ± 188.33	903.11 ± 138.14	[97.45 ; 108.95]	103.04
$t_{1/2}$ (h)	3.66 ± 3.60	3.79 ± 5.54	[72.55 ; 95.26]	83.13

Pharmacokinetic results and statistical analysis of comparative study for **3-OH-Pravastatin** (log-transformed data)				
Parameters	PRAVASINE ® 40 mg	Fenofibrate-Pravastatin 160-40mg	Bioequivalence 90 %CI	Point estimate
AUC_{∞} (ng.h/ml)	171.51 ± 86.18	227.06 ± 114.58	[120.91 ; 150.11]	134.72
AUC_{τ} (ng.h/ml)	158.85 ± 81.80	213.54 ± 101.86	[124.77 ; 151.81]	137.62
C_{max} (ng/ml)	63.42 ± 30.57	89.74 ± 43.51	[128.77 ; 157.05]	142.21
C_{min} (ng/ml)	0.32 ± 0.12	0.35 ± 0.17	[92.15 ; 119.43]	104.91
t_{max} (h)	2.15 ± 0.83	2.13 ± 0.56	NS	-
F (%)	975.32 ± 237.12	1007.18 ± 212.43	[96.86 ; 110.59]	103.49
$t_{1/2}$ (h)	3.87 ± 3.40	3.60 ± 3.22	[71.41 ; 121.10]	92.81

The findings of the study show that the systemic exposure (estimated by AUC and C_{max}) to fenofibrate observed with Pravafenix is similar to that observed in subjects treated with Lipanthyl alone. Significantly higher systemic exposure to pravastatin (30-40%) is observed with the combination when compared to the administration of pravastatine alone. The specific mechanism for such interaction between fenofibrate and pravastatin remains unknown, but it is speculated that competition with or modulation of OATP1B1or P-glycoprotein may play a role. The CHMP expressed their concern regarding the design of study SMB-FENOPRA-SS31 due to the use of Pravafenix as a comparator in the third arm of the study. The differences in the biopharmaceutical performances of the formulations (Pravafenix, Lipanthyl, Pravasine) could introduce a bias in the estimation of the interaction potential. A free co-administration of Lipanthyl 160 mg and Pravasine 40 mg (instead of Prafavenix) in the comparator arm could have been the appropriate alternative. Furthermore, the conduct of the study under fed conditions might also introduce a bias in the estimation of the drug-drug interaction potential as food intake does impact noticeably and differently the bioavailability of pravastatin and fenofibrate. Systemic exposure to fenofibrate is enhanced by food-intake. Conversely, pravastatin bioavailability is noticeably reduced by food-intake. Therefore, the outcome of study SMB FEPRA-SS-031 suggest that co-administration of fenofibrate enhances moderately systemic exposure to pravastatin (30-40%). The CHMP requested further clarification on the results of this study and overall impact on the interactions between the monocomponents of this FDC. In response, further arguments and results of supportive studies SMB-FEPRA-SD081, SMB-FEPRA-SS071, SMB-FEPRA-SS072, although not significantly relevant, have been presented. Considering that the FDC and monocomponent drug products perform differently and are impacted differently by food intake, formulation effect and food effect are confounding factors precluding any strong statement regarding the interaction potential. However, it is acknowledged that the outcome of the study SMB-FENOPRAVA-SS031, even with its limitation, revealed no marked potential for interaction between pravastatin and fenofibrate. In addition, this statement was confirmed by the published literature data.

Pharmacokinetics using human biomaterials

No specific studies have been conducted examining pharmacokinetics of Pravafenix using human biomaterials.

2.4.3. Pharmacodynamics

Mechanism of action

Pravastatin. Pravastatin sodium is a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin), which reduces cholesterol biosynthesis by interfering with the conversion of HMG-CoA to mevalonate, an early rate-limiting step in cholesterol biosynthesis. Pravastatin reduces also the activity of the cholesteryl ester transfer protein, a plasma glycoprotein responsible for the transfer of high density lipoprotein cholesterol (HDL-C) esters to very low density lipoprotein (VLDL) and LDL in the reverse cholesterol transport pathways. It has been suggested that HMG-COA reductase inhibitors such as pravastatin inhibit the production of LDL-C directly by inhibiting the hepatic synthesis of VLDL-cholesterol (VLDL-C), a precursor for LDL-C.

Fibrates represent one of the older classes of lipid-lowering drugs and exert effects mainly by activating the peroxisome proliferator-activated receptor-alpha (PPAR-alpha). Through activation of PPAR-alpha fenofibrate increases the lipolysis and elimination of atherogenic triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein CIII.

Primary and secondary pharmacology

No pharmacodynamic studies have been performed with the fenofibrate/pravastatin FDC itself since the properties of the individual compounds are not expected to be different from those observed when both components are given together as a free combination. The individual pharmacodynamic profiles for fenofibrate and pravastatin are well established. The discussion of the pharmacodynamics of both active substances is based on the literature overview.

The pharmacodynamics properties of each component support the interest of combining pravastatin with fenofibrate. The mechanisms of action of both drugs are expected to be, at least partly, complementary. With the FDC, beneficial effects on the 3 biological defects of mixed dyslipidaemia, i.e. increased LDL-C and TG and decreased HDL-C, can be anticipated. Thus, this combination is from a theoretical point of view of clinical interest, since an additional effect on lipid parameters could be expected. Nevertheless, the CHMP noted that such combination using in particular fenofibrate must be devoid of potentially deleterious interactions that could have an impact on the efficacy and safety profile of the product. Fenofibrate has a low potential for drug-drug interaction since it does not undergo a significant metabolism by cytochrome P450. In addition, pravastatin metabolism is not mediated by CYP450. Therefore, drug-drug interaction potential of the active ingredients of the FDC under review appears to be limited. A complete pharmacokinetic programme was submitted for this FDC marketing authorisation application. For further details please refer to the sections on Pharmacokinetics and Clinical efficacy and safety.

2.4.4. Discussion on clinical pharmacology

The individual pharmacokinetics for pravastatin and fenofibrate are well established and no further investigations are considered necessary. Single strength is claimed for Pravafenix (160 mg fenofibrate/40 mg pravastatin). There is a significant reduction in pravastatin pharmacokinetics with food and a significant increase in fenofibrate pharmacokinetics with food. The FDC is recommended to be taken with food because the bioavailability of fenofibrate is increased when administered with food. Although the bioavailability of pravastatin is reduced when taken with food, the lipid-lowering efficacy is not altered, as documented in the published literature. Indeed, the harmonised SmPC of pravastatin allows administration with or without food. Recommendations regarding the use of the fixed combination in special population are derived from the experience with the use of each component separately. Dose adjustment is not necessary in the elderly patients for the actives substances of the FDC, but recommendations before the initiation of therapy are provided in the Pravafenix SmPC. Review of the potential new interactions has not been conducted but the already identified interactions mentioned in the SmPCs of pravastatin and fenofibrate are adequately reflected in the SmPC of the FDC. In summary, it can be concluded that the clinical pharmacology of the FDC has been sufficiently documented, and the questions related to the bioequivalence studies have been clarified.

2.4.5. Conclusions on clinical pharmacology

The individual pharmacokinetics for pravastatin and fenofibrate are well established and no further comments are necessary. Single strength is claimed for the FDC, Pravafenix (160 mg fenofibrate/40 mg pravastatin). The individual pharmacodynamics for fenofibrate and pravastatin are well established. The mechanisms of action of both drugs are expected to be, at least partly, complementary. The discussion of the clinical pharmacology of both active substances is based on the results of a literature search.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

No dose response study has been performed and this is justified since the efficacy for both substances have been well characterised for numerous years.

Rational for the choice of pravastatin and fenofibrate dosage
Pravafenix is developed as an orally-administered fixed combination of pravastatin and fenofibrate. Single strength combination of 40 mg pravastatin and 160 mg fenofibrate has been developed. The product is intended as a second-line treatment (in inadequately controlled patients) and thus, the statin dose should be the maximal effective and tolerated dose. It should be also highlighted that the only studied starting and maintenance dose was 40 mg daily for cardiovascular prevention. Thus, the choice of a 40 mg maximal daily dose of pravastatin and a fenofibrate (160 mg) for the clinical development is justified, and a single strength for Pravafenix is acceptable.

2.5.2. Main study(ies)

The phase III clinical development programme in patients with mixed hyperlipidaemia included 4 main studies (see table below), of which two were performed in Europe:
Study SMB-FEBRA-0303 was performed in patients with mixed hyperlipidaemia and high cardiovascular risk and study FENOPRA-III-06-01 was performed in type 2 diabetic patients with mixed hyperlipidaemia. One confirmatory study performed in the United States: Sc-PRAVA-06-02. The fourth study performed in Europe, FENOPRA-III-05-1, was a 24-week open-label safety study. All phase III controlled efficacy study were conducted using the final formulation.

SMB-FEPRA-0303: A PHASE III, TWO-ARMED, RANDOMISED, DOUBLE-BLIND, DOUBLE-DUMMY, PARALLEL STUDY TO COMPARE THE THERAPEUTIC EFFICACY ON 12 WEEKS OF ONE COMBINATION (FENOFIBRATE/PRAVASTATIN 160-40 MG) VERSUS PRAVASTATIN 40 MG ALONE, FOLLOWED BY AN OPEN-LABELLED SAFETY PHASE OF THE COMBINATION ALONE, ON 52 WEEKS, IN HIGH RISK PATIENTS WITH COMBINED HYPERLIPIDEMIA.

This study was designed to demonstrate the superiority of the FDC of fenofibrate/pravastatin 160mg/40mg in terms of non HDL-C, LDL, TG reduction from baseline and of HDL-C increase.

FENOPRA-III-06-01: A PHASE III, FOUR-ARMED, RANDOMIZED, DOUBLE BLIND, PARALLEL STUDY TO COMPARE THE EFFICACY AND SAFETY IN TYPE 2 DIABETIC PATIENTS WITH COMBINED HYPERLIPIDEMIA OF A 12-WEEK ADMINISTRATION OF FENOFIBRATE 160MG/PRAVASTATIN 40MG COMBINATION VERSUS SIMVASTATIN 20MG IN PATIENTS WITHOUT CARDIOVASCULAR DISEASE (CVD) (GROUP 1) AND OF FENOFIBRATE 160 MG/PRAVASTATIN 40MG COMBINATION+EZETIMIBE 10MG VERSUS SIMVASTATIN 20MG+EZETIMIBE 10MG IN PATIENTS WITH CVD (GROUP 2), FOLLOWED BY A 12-WEEK SAFETY PHASE OF FENOFIBRATE 160MG/PRAVASTATIN 40MG COMBINATION IN GROUP 1 AND FENOFIBRATE 160MG/PRAVASTATIN 40MG COMBINATION+EZETIMIBE 10MG IN GROUP 2.

This study was designed to assess the efficacy in type II diabetes patients with mixed dyslipidaemia of Pravafenix 160/40mg FDC versus simvastatin 20mg in patients without cardiovascular disease (CVD) (stratum 1) and Pravafenix 160mg/40mg FDC + ezetimibe 10mg versus simvastatin 20mg + ezetimibe 10mg in patients with CVD (startum 2).

Sc-PRAVA-06-02: A MULTI-CENTER, PROSPECTIVE, LONGITUDINAL, RANDOMIZED, DOUBLE-BLIND, PHASE III STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DAILY ADMINISTRATION OF PRAVASTATIN 40MG OR FENOFIBRATE 160MG OR PRAVAFEN (COMBINATION OF PRAVASTATIN AND FENOFIBRATE 40/160MG) FOR 12 WEEKS, FOLLOWED BY A 52-WEEK OPEN-LABEL SAFETY PHASE OF PRAVAFEN ALONE, IN THE TREATMENT OF COMBINED HYPERLIPIDEMIA.

This study was not performed in the target population. Indeed, recruited patients were not at high cardiovascular risk. Thus, the contribution of this study to the current application is limited.

Studies SMB-FEPRA-0303 is considered to be the main trial for this application. Thus, the majority of the clinical chapters below refer to the conduct of study SMB-FEPRA-0303 and data from other studies are quoted when and as appropriate to support the scientific discussion.

The overall summary of these studies is presented in the table below.

Study ID	No. of study centres / locations	Design	Treatment	Nº of patients (ITT) for efficacy	Duration	Gender (ITT) M/F (%); Age (ITT) Mean±sd	Diagnosis Incl. criteria	Primary Endpoint
SMB-FEPRA-0303	41 centres/3 countries (France, Poland and Belgium)	Two-arm, randomised, parallel with a 8-week run-in period on Pravasine 40mg/d a 12-week double-blind treatment period, and a 52-week open-label extension period	Pravafenix 160-40 mg/d Pravasine ® 40 mg/d	120 119	64 weeks	69.2/30.8 ; 57.8± 9.4 71.4/28.6; 57.9±9.1	High vascular risk patients according to the NCEP ATP III definitions with a mixed dyslipidemia	Mean percent change in non-HDL-C from baseline * to week 12/end-of-efficacy period
FENOPRA III-06-01	73 centres / 6 countries (France, Norway, Romania, Poland, Hungary, and Germany)	Four-arm , randomized, parallel with a 6-week run-in period on SIMVA 20 mg, a 12-week double-blind treatment period, and a 12-week open-label extension period	Pravafenix 160-40 mg/d Zocor ® 20 mg/d Pravafenix 160-40 mg/d + ezetimibe 10 mg Zocor ® 20 mg/d + ezetimibe 10 mg	144 145 133 133	24 weeks	45.8/54.2; 56.0±8.4 51.0/49.0; 61.4±8.3 44.4/55.6; 57.2±9.5 48.1/51.9; 60.6±7.5	Type 2 diabetic patients as defined by the WHO and mixed dyslipidemia	Mean percent change in non-HDL-C from baseline** to week 12/end-of-efficacy period
Sc-PRAVA-06-02	76/one country (USA)	Three-arm , randomized, parallel with a 8-week run-in period on Pravastatin 40 mg/d; a 12-week double-blind treatment period, and a 52-week open-label extension period	Pravafenix 160-40 mg/d Pravachol ® 40 mg/d Fenofibrate Galephar 160 mg/d	238 111 119	64 weeks	48.7/51.3; 53.6±9.2 53.2/46.8; 54.6±8.7 42.0/58; 54.0±10.2	Mixed dyslipidemia	Mean percent change in non-HDL-C from baseline*** to week 12/end-of-efficacy period
FENOPRA III-05-01	56/two countries (Czech Republic and France)	Open-label phase III, to evaluate the safety of the Fenofibrate/Pravastatin 160-40 mg combination during 24 weeks	Pravafenix 160-40 mg/d	307	24 weeks	67.4/32.6; 59.9 ±8.7	High or very high vascular risk patients according to the NCEP ATP III definitions with a mixed dyslipidemia	Primary endpoint: Safety parameters Secondary efficacy endpoint: Mean percent change in non-HDL-C from baseline**** to week 24/end-of-study

Methods

Study Participants

Patients enrolled in study SMB-FEPRA-0303 were: i) male and female, aged 18 years or older, ii) high cardiovascular risk patients as defined by the NCEP ATP III with documented mixed dyslipidaemia (multiple risk factors that confer a 10-year risk for CHD > 20% (calculated according to the Framingham tables) or coronary heart disease (CHD) or other clinical forms of atherosclerotic disease or diabetes.
Inclusion lipid parameters: patients with LDL-C $\geq$ 100mg/dL AND 150 < TG>400mg/dL at the end of the selection period under pravastatin 40 mg/day.

Main exclusion criteria were: Secondary or iatrogenic dyslipidemia, hyperlipidemia type I-IIa-IV-V, TG > 400 mg/dl, abnormal liver function (hepatocellular insufficiency, chronic or active liver disease, sustained elevation of serum liver enzymes > 2 x UNL), CPK > 3 x UNL, abnormal renal function (clearance of creatinine < 50 ml/mn) or any renal disease likely to lead to renal dysfunctions, uncontrolled primary hypothyroidism, acute cardiovascular episode within the 6 months prior to the start of the trial, uncontrolled hypertension, and other criteria.

This study comprised of the following periods:
Selection period: 8 weeks during which the patients were stabilised on PRAVASINE 40 mg/day.
Efficacy phase: 12 weeks during which the patients were randomised to one of the two possible treatments (fenofibrate/pravastatin 160-40 mg or pravastatin 40 mg). Patients were randomised either to fenofibrate/pravastatin 160/40mg per day or pravastatin 40mg per day from the first day of the efficacy phase (from V1 to V4 - 12 weeks). They received a capsule of placebo at the same time.
Safety phase: Additional period of 52 weeks under the combination product (fenofibrate/pravastatin 160-40 mg) whichever the treatment taken during the efficacy phase.

W-8 open-label W0
Selection period– 8 weeks
Pravastatin 40 mg daily

W0 double-blind, double-dummy W12
Efficacy Phase– 12 weeks
Pravastatin 40 mg and placebo, or fenofibrate/pravastatin 160-40 mg and placebo

W12 open-label W64
Safety Phase – 52 weeks
Fenofibrate/pravastatin 160-40 mg daily

Treatments

Test product: fenofibrate/pravastatin 160-40 mg, one capsule, taken once a day orally, containing 160 mg of fenofibrate and 40 mg of pravastatin.

Reference therapy: PRAVASINE 40 mg, one tablet, taken once a day, orally, containing 40 mg of pravastatin.

Objectives

Study SMB-FEPRA-0303 was designed to demonstrate the superior efficacy of fenofibrate 160 mg and pravastatin 40 mg FDC (Pravafenix) compared with Pravastatin 40 mg monotherapy in high cardiovascular risk patients with mixed dyslipidemia, as measured by the mean percent change in non-HDL-C at the end of the 12-week efficacy period. In addition, the study design allowed for a comparison of safety and tolerability of fenofibrate 160 mg and pravastatin 40 mg FDC with pravastatin 40 mg monotherapy. The CHMP acknowledged that the objectives of this clinical study are deemed appropriate to show the superiority of Pravafenix over pravastatin in the claimed target indication.

Outcomes/endpoints

The primary and secondary endpoints of study SMB-FEPRA-0303 can be summarised as follows.
Primary endpoint: Mean percent changes in plasma non-HDL cholesterol levels at the end of the efficacy period compared to the baseline.

Secondary endpoints:

- Percentage of patients who achieve the therapeutic goals concerning the non-HDL and LDL levels, as defined in the NCEP ATP III
- Evolution of the LDL levels
- Evolution of the following other lipidemic parameters levels: HDL, TG, total cholesterol
- Evolution of Apo A, Apo B levels
- Evolution of C Reactive Protein (CRP) values
- Evolution of Fibrinogen values
- Differences in estimated cardiovascular risk for myocardial infarction (PROCAM risk calculator)

Sample size

Sample size calculation was done in order to demonstrate the superiority of the combination fenofibrate/pravastatin 160/40 mg *vs* pravastatin 40 mg for the analysis of the primary efficacy endpoint. As reference data on non-HDL (LDL + VLDL) cholesterol levels were not available, the worst case was adopted by taking the hypotheses based on the LDL cholesterol levels for the effect of the combination fenofibrate/pravastatin. A difference between treatment groups in mean percent changes in plasma LDL cholesterol level between baseline (after 8 weeks under pravastatin 40 mg/day) and visit V4 (W12) of 6% is considered as clinically meaningful difference. A sample size of 140 patients (70 per treatment group) allowed for a statistical power of at least 90% for the detection of a difference Δ= 6% between treatment groups in mean percent changes (group 1: $\mu 1$ = - 20%, group 2: $\mu 2$ = - 26%), considering a standard deviation of 20 mg/dl and using a one-tailed test on the α= 5% significance level. Statistical power obtained for N = 140 patients from calculation based on LDL cholesterol level was a fortiori sufficient considering the non-HDL cholesterol level according to the previous argument. A calculation of the power a posteriori based on the ApoB parameter was made to confirm this argument. In addition, allowing for a drop-out rate of about 40% of patients before the end of the total safety period (64 weeks), a total of 240 patients were required to be randomised in this trial.

Randomisation and Blinding (masking)

The list of randomisation was issued using computer software. Treatments and the corresponding decoding envelopes were prepared according to this list. Treatments were randomised before being packaged and were assigned by chronological order to the centres. The investigators dispensed the study treatments to patients according to the treatment numbers received at their centre.

Patients received a capsule of placebo of identical properties as the active drug at the same time (double placebo). Thus, patients took 2 capsules at each evening meal. In order to maintain the blind during the treatment period for each patient, lipid parameters obtained from blood samples from baseline to final visit were kept in blinded condition until the database was closed. Neither the investigator nor the sponsor of the study was informed during the study. The blinded conditions and the randomisation technique are considered appropriate. Lipid parameters were also measured at randomisation in a blinded manner.

Statistical methods

For the assessment of the mean percent change *vs* baseline for the lipid parameters, two different statistical methods were used: i) a mean change calculated and ii) a Least Squares Mean (LS Mean) derived from the ANCOVA test. Intent-to-treat (ITT) population, which consisted of all randomised patients who had at least one on-therapy data value for efficacy parameters, was used for efficacy analyses. Per Protocol (PP) population was also used. A two-sided statistical test with alpha =5% significance level was used for primary efficacy endpoint. All other statistical tests were two-tailed and the level of significance was set at 0.05. The CHMP considered that the performed statistical analyses are appropriate. It is adequate to report changes in lipids as mean percentage change from baseline.

Results

Participant flow

Overall, 480 patients were screened based on established inclusion and exclusion criteria in study SMB-FEPRA-0303. At baseline (Week 0), 248 patients (*safety* population) were randomised into one of both treatment groups of the efficacy phase, i.e. fixed dose combination fenofibrate/pravastatin 160/40 mg or reference (pravastatin 40 mg). At the end of the *efficacy* phase (Week 12), all the

patients took fenofibrate/pravastatin 160-40 mg (patients who completed reference treatment were switched to fenofibrate/pravastatin 160-40 mg). The overview of participant flow is given in the table below.

PIVOTAL TRIAL SMB-FEPRA-0303		
	Fenopra*	**Prava**
Selected (n=2880)	**480**	
Reasons for non inclusion		
Not meeting the selection or inclusion criteria	190	
Abnormal laboratory result	18	
Adverse event	12	
Withdrawal of consent	11	
Other reason	1	
Randomised	**248**	
	123	125
Discontinued during W0-W12	**15**	**9**
Reasons		
Adverse event	5	3
Abnormal laboratory result	3	1
Protocol violation	2	2
Withdrawal of consent	3	3
Lost to follow-up	2	
Completed the efficacy double-blind period	**224**	
	108	116
Discontinued before final visit	**13**	
Reasons		
Adverse event	3	
Abnormal laboratory result	2	
Protocol violation	2	
Withdrawal of consent	2	
Lost to follow-up	3	
Other	3	
Completed the W24	**211**	

**Fenopra = Fenofibrate+pravastatin combination*

Recruitment

Study SMB-FEPRA-0303 was conducted in 41 active centers: 26 in France, 10 in Poland and 5 in Belgium from 23 October 2003 (first inclusion) to 27 September 2006 (last follow-up visit).

Conduct of the study

The first amendment of study SMB-FEPRA-0303 protocol dated August 26, 2003 was approved before the first inclusion of the first patient. This change referred to assuring consistency regarding the date of the first ECG (to be performed at V1 and not at VS). In France, 3 other amendments were written in order to compensate the insufficient recruitment of patients: Amendment No. 2 dated June 14, 2004: update of the investigators participating in the study, new prospective investigators and extension of the inclusion period. Amendment No. 3 dated August 23, 2004: update of the investigators participating in the study. Amendment No. 4 dated January 3, 2005: extension of the inclusion period. In Poland, Amendment No. 2 dated March 19, 2004 concerned the update of contact details for safety reporting. No other amendment was required in Belgium. The CHMP concluded that the protocol amendments do not appear to have any influence on the validity of the study data and the provided analysis.

Baseline data

Summary of demographic data in study SMB-FEPRA-0303 at selection visit VS – ITT population in the efficacy phase is provided in the table below.

Treatment groups		Fenofibrate/pravastatin 160-40 mg N = 120	Pravastatin 40 mg N = 119	Total N = 239
Gender				
female	N (%)	37 (30.83%)	34 (28.57%)	71 (29.71%)
male	N (%)	83 (69.17%)	85 (71.43%)	168 (70.29%)
Age (years)	m ± sd	57.75 ± 9.41	57.87 ± 9.10	57.81 ± 9.24
Age class - years				
< 65 years	N (%)	84 (70.00%)	91 (76.47%)	175 (73.22%)
≥ 65 years	N (%)	36 (30.00%)	28 (23.53%)	64 (26.78%)
Height (cm)	m ± sd	167.76 ± 8.82	169.46 ± 8.58	168.61 ± 8.72
Weight (kg)	m ± sd	82.43 ± 12.74	86.09 ± 15.06	84.25 ± 14.03
Waist circumference (cm) m ± sd		100.11 ± 10.70	102.43 ± 11.13	101.28 ± 10.96
BMI (kg/m^2)	m ± sd	29.30 ± 4.15	29.92 ± 4.40	29.61 ± 4.28

The CHMP noted that the elderly (≥ 65 years old) represented 26.78% of the included compared to 73.22% for patients < 65 years old). Overall, only 36 patients older than 65 years have been treated with the FDC. No patient older than 75 years has been treated with the FDC. Otherwise, there was no major imbalance between the treatment groups.

Numbers analysed

A total of 480 patients were selected and 248 patients were randomised in order to obtain 211 patients who completed study SMB-FEPRA-0303.

- Analysed in the Efficacy phase (V1-V4):
Safety analysis: 248 patients (fenofibrate/pravastatin 160-40 mg group: 123, PRAVASINE® 40 mg group: 125)
Efficacy analyses: ITT: 239 patients (fenofibrate/pravastatin 160-40 mg group: 120, PRAVASINE® 40 mg group: 119)
Per Protocol: 209 patients (fenofibrate/pravastatin 160-40 mg group: 101, PRAVASINE® 40 mg group: 108)
- Analysed in the Safety phase (V4-V9):
Safety analysis: 224 patients
Efficacy analyses: ITT: 223 patients
Per Protocol: 181 patients

Outcomes and estimation

Primary endpoint

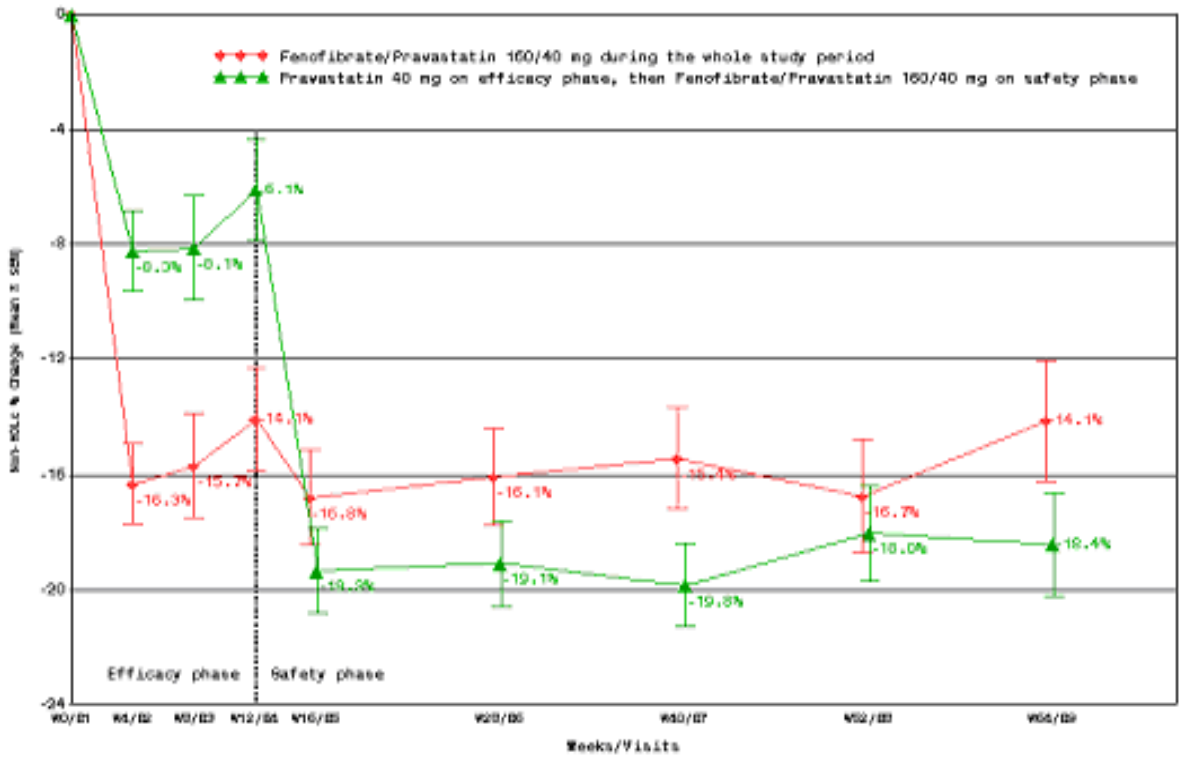
Results on the analysis of the primary endpoint in study SMB-FEPRA-0303 are presented in the below table and figure.

Mean percent changes in **non-HDL cholesterol levels** from baseline to the end of the efficacy phase (12 weeks) - LOCF method – ITT analysis

Treatment groups		Fenopra N = 120	Prava N = 119	P-value (Fenopra/Prava)
Mean percent change between baseline* and Week 4 (%) +	m ± sem	-16.30 ± 1.39	-8.25 ± 1.40	
	p-value~	< 0.0001	< 0.0001	< 0.0001
Mean percent change between baseline* and Week 8 (%) +	m ± sem	-15.69 ± 1.81	-8.14 ± 1.81	
	p-value~	< 0.0001	< 0.0001	0.004
Mean percent change between baseline* and Week 12 (%) +	m ± sem	-14.07 ± 1.78	-6.11 ± 1.79	
	p-value~	< 0.0001	< 0.001	0.002

* Mean of the values recorded at the BS2 and B1 laboratory exam (after 8 weeks under Pravastatin 40 mg/day)
+ Adjustment on the non-HDLc level at baseline (covariate) with an analysis of covariance.
~ Statistical test assessing the significance of the mean percent change between baseline and each visit of the efficacy phase in each treatment group.

Mean percent change (%) from baseline in non HDL-cholesterol during the efficacy and safety phase in study SMB-FEPRA-0303



The maximum effect was observed after 4 weeks of treatment. The decrease of non HDL-C levels from baseline to week 12 was statistically significant. The decrease of non-HDLc levels observed after the 12-week efficacy phase was maintained after 64 weeks for patients taking fenofibrate/pravastatin 160-40 mg during the whole study (p = 0.352).

Secondary endpoints

LDL-C levels

Mean percent changes in LDL cholesterol levels from baseline to the end of the efficacy phase (12 weeks) in study SMB-FEPRA-0303 are presented in the table below.

Treatment groups	Fenopra N = 120	Prava N = 119	P-value (Fenopra/Prava)
Mean percent change between baseline* and Week 4 (%) +			
m ± sem	-11.75 ± 1.53	-8.09 ± 1.54	
p-value~	< 0.0001	< 0.0001	0.093
Mean percent change between baseline* and Week 8 (%) +			
m ± sem	-12.65 ± 1.72	-9.12 ± 1.72	
p-value~	< 0.0001	< 0.0001	0.148
Mean percent change between baseline* and Week 12 (%) +			
m ± sem	-11.73 ± 1.75	-5.87 ± 1.76	
p-value~	< 0.0001	0.001	0.019

* Mean of the values recorded at the BS2 and B1 laboratory exams (after 8 weeks under Pravastatin 40 mg/day)
+ Adjustment on the LDLc level at baseline (covariate) with an analysis of covariance.
~ Statistical test assessing the significance of the mean percent change between baseline and each visit of the efficacy phase in each treatment group.

HDL-C levels

Mean percent changes in HDL cholesterol levels from baseline to the end of the efficacy phase in study SMB-FEPRA-0303 are presented in the table below.

Treatment groups	Fenopra N = 120	Prava N = 119	P-value (Fenopra/Prava)
Mean percent change between baseline* and Week 4 (%)+			
m ± sem	+5.28 ± 0.88	+2.00 ± 0.88	
p-value~	< 0.0001	0.024	0.009
Mean percent change between baseline* and Week 8 (%)+			
m ± sem	+6.62 ± 1.12	+1.86 ± 1.12	
p-value~	< 0.0001	0.098	0.003
Mean percent change between baseline* and Week 12 (%)+			
m ± sem	+6.48 ± 1.12	+2.27 ± 1.13	
p-value~	< 0.0001	0.045	0.009

** Mean of the values recorded at the BS2 and B1 laboratory exams (after 8 weeks under PRAVASINE® 40 mg/day)*
+ Adjustment on the HDLc level at baseline (covariate) with an analysis of covariance.
~ Statistical test assessing the significance of the mean percent change between baseline and each visit of the efficacy phase in each treatment group.

TG levels

Mean percent changes in triglyceride levels from baseline to the end of the efficacy phase in study SMB-FEPRA-0303 are presented in the table below.

Treatment groups	Fenopra N = 120	Prava N = 119	P-value (Fenopra/Prava)
Mean percent change between baseline* and Week 4 (%)+			
m ± sem	-30.13 ± 2.52	-7.57 ± 2.53	
p-value~	< 0.0001	0.003	< 0.0001
Mean percent change between baseline* and Week 8 (%)+			
m ± sem	-26.15 ± 4.66	-1.44 ± 4.68	
p-value~	< 0.0001	0.758	< 0.001
Mean percent change between baseline* and Week 12 (%)+			
m ± sem	-22.59 ± 4.37	-2.03 ± 4.39	
p-value~	< 0.0001	0.645	0.001

** Mean of the values recorded at the BS2 and B1 laboratory exams (after 8 weeks under PRAVASINE® 40 mg/day)*
+ Adjustment on the triglyceride level at baseline (covariate) with an analysis of covariance.
~ Statistical test assessing the significance of the mean percent change between baseline and each visit of the efficacy phase in each treatment group.

ApoA1 levels

Analysis of ApoA1 levels from baseline to B4/W12 in study SMB-FEPRA-0303 is presented in the table below.

Treatment groups	Fenopra N = 120	Prava N = 119	P-value (Fenopra/Prava)
ApoA1 level at baseline (g/l)*			
N	120	119	
m ± sd	1.38 ± 0.18	1.38 ± 0.17	
CI 95%#	[1.35 , 1.41]	[1.35 , 1.41]	
ApoA1 level at B4/W12 (g/l)			
N	109	115	
m ± sd	1.45 ± 0.23	1.41 ± 0.19	
CI 95%#	[1.40 , 1.49]	[1.37, 1.44]	
Mean percent change between baseline*			
and B4/W12 (%)+ N	109	115	
m ± sem	+5.46 ± 0.99	+2.82 ± 0.97	
p-value~	< 0.0001	0.004	0.058

** Mean of the values recorded at the BS2 and B1 laboratory exams (after 8 weeks under PRAVASINE® 40 mg/day)*
 # 95% Confidence Interval for the mean assuming a normal distribution.
+ Adjustment on the ApoA1 level at baseline (covariate) with an analysis of covariance.
~ Statistical test assessing the significance of the mean percent change between baseline and B4/W12 in each treatment group.

Other lipid parameters

Levels of TC, apoB, apoB/apoA1, fibrinogen and hsCRP were significantly influenced by the Pravafenix therapy compared to pravastatin monotherapy.

The CHMP assessed the above described results in the following manner:
LDL-C. After 12 weeks of treatment with Pravafenix, a significant ($p < 0.001$) decrease of 6% in LDL-C levels in comparison with baseline was observed in pravastatin treated patients; this decrease may indicate that patients were probably not pravastatin failures at the time of randomisation. Results were not significant after 4 and 8 weeks of treatment and became significant after 12 weeks of treatment.

HDL-C. The addition of fenofibrate 160mg to pravastatin 40mg resulted in an increase of HDL-C level of + 6.5% in the FDC group compared to +2% in the pravastatin group. This is not surprising as pravastatin is not intended to increase HDL-C. The difference between the 2 groups of treatment is significant.

TG. The addition of fenofibrate 160mg to pravastatin 40mg resulted in a reduction of TG of -30% to a clinically relevant extent that was more pronounced after 4 weeks of treatment than after 12 weeks of treatment. In the pravastatin group, the decrease from baseline was only significant after 4 weeks of treatment (-7.6%). As expected, the difference between groups is statistically significant in favour of the FDC.

Apo A1. An increase in ApoA1 is observed in each treatment group after 12 weeks. However, the difference between groups is not statistically different but is in favour of the FDC (p=0.058).

Ancillary analyses

The CHMP acknowledged that post hoc pooled analysis of SMB-FEPRA-0303 and Sc-PRAVA-06-02 studies (that used the same comparator pravastatin 40 mg) derived from Integrated Summary of Efficacy (ISE) performed for the U.S submission have been provided. The overall recipient is 707 patients out of the short term efficacy dataset (n=996, 71%). Subgroup analyses from pooled analyses were performed to look for possible differences in treatment effect across groups.
The following subgroups were analysed:
- Age group (<65, ≥65 and ≤75, and > 75 years);
- Gender (male and female);
- Race (Black and non-Black);
- Baseline LDL-C category (≥100 a <130 mg/dL; ≥130 to <160 mg/dL, and ≥160 mg/dL);
- Baseline TG category (<200 mg/dL; ≥200 to < 400 mg/dL; and ≥400 mg/dL); and
- Baseline LDL-C and TG category.

Nevertheless, no significantly relevant information is obtained from these groups analysis.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial SMB-FEPRA-0303, summary of Main Efficacy Results

Title: A phase III, two-armed, randomised, double-blind, double-dummy, parallel study to compare the therapeutic efficacy on 12 weeks of one combination (Fenofibrate/Pravastatin 160-40 mg) versus Pravastatin 40 mg alone, followed by an open-labelled safety phase of the combination alone, on 52 weeks, in high risk patients with combined hyperlipidemia.		
Study identifier	SMB-FEPRA-0303	
Design	Multicentre, phase III randomised, 12-week parallel study, followed by a 52-week safety phase of the combination alone.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 weeks 8 weeks 52 weeks
Hypothesis	Superiority	
Treatments groups	Fenopra	Fenofibrate/Pravastatin 160-40 mg, one capsule, taken once a day orally, during 12 weeks – 123 patients
	Prava	PRAVASINE 40 mg, one tablet, taken once a day, during 12 weeks – 125 patients

Endpoints and definitions	Primary endpoint	Mean change in non-HDLc	Mean percent changes in non-HDL cholesterol levels from baseline to the end of the efficacy phase (12 weeks)
	Secondary endpoints	Mean change in LDL, HDL, TG, TC, ApoA1; ApoB, ApoB/ApoA1, fibrinogen, HsCRP	The mean percent changes from baseline in other biological parameters levels at the end of the efficacy phase (LDLc, HDLc, triglycerides, total cholesterol, $ApoA_1$, ApoB, ratio $ApoB/ApoA_1$, fibrinogen and HsCRP)
	Secondary endpoints	Achievement of the therapeutic goals	The proportion of patients achieving the therapeutic goals defined by NCEP ATP III at the end of the efficacy phase
	Secondary endpoints	Mean change in 10-year CHD risk	The mean percent change in estimated 10-year cardiovascular risk for myocardial infarction (PROCAM risk calculator) at the end of the efficacy phase compared to the estimated risk at baseline.
	Safety endpoints	Adverse events, withdrawals or drop-out rate, laboratory data, vital signs, physical examination and ECG.	
Database lock	13-01-2009		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	***Safety analysis***: 248 patients (Fenofibrate/Pravastatin 160-40 mg group: 123, PRAVASINE 40 mg group: 125) ***Efficacy analyses***: **ITT**: 239 patients (Fenofibrate/Pravastatin 160-40 mg group: 120, PRAVASINE 40 mg group: 119) **Per Protocol**: 209 patients (Fenofibrate/Pravastatin 160-40 mg group: 101, PRAVASINE 40 mg group: 108) ***Baseline****: Mean of the values recorded after 7 and 8 weeks under PRAVASINE 40 mg/day* ***End of efficacy endpoint****: After 12 weeks of treatment*

Descriptive statistics and estimate variability	Treatment group	**Fenopra**	**Prava**	**P-value Fenopra/Prava**
	Number of subject	**N = 120**	**N = 119**	
	Non-HDLc level at baseline (mg/dl) m ± sd	182.57 ± 29.93	186.66 ± 31.37	
	CI 95%	[177.16 , 187.98]	[180.97 , 192.35]	
	Non-HDLc level at Week 12 (mg/dl) m ± sd	155.88 ± 44.71	174.26 ± 37.50	
	CI 95%	[147.79 , 163.96]	[167.45 , 181.07]	
	Non-HDLc Mean percent change between baseline and Week 12 (%) m ± sem	-14.07 ± 1.78	-6.11 ± 1.79	

	p-value	< 0.0001	< 0.001	**0.002**
Effect estimate per comparison	LDLc Mean percent change between baseline and Week 12 (%)	**Fenopra** m ± sem		-11.73 ± 1.75
		Prava m ± sem		-5.87 ± 1.76
		P-value Fenopra/Prava		**0.019**
	HDLc Mean percent change between baseline and Week 12 (%)	**Fenopra** m ± sem		+6.48 ± 1.12
		Prava m ± sem		+2.27 ± 1.13
		P-value Fenopra/Prava		**0.009**
	TG Mean percent change between baseline and Week 12 (%)	**Fenopra** m ± sem		-22.59 ± 4.37
		Prava m ± sem		-2.03 ± 4.39
		P-value Fenopra/Prava		**0.001**
	TC Mean percent change between baseline and Week 12 (%)	**Fenopra** m ± sem		-9.88 ± 1.37
		Prava m ± sem		-4.45 ± 1.38
		P-value Fenopra/Prava		**0.006**
Notes	The non-HDLc was significantly more reduced with Fenofibrate/Pravastatin 160-40 mg than with PRAVASINE 40 mg after 12 weeks (p = 0.002). This was already observed after 4 and 8 weeks of treatment. After 12 weeks, the LDLc (-11.7%) and total cholesterol (-9.9%) were significantly more reduced with Fenofibrate/Pravastatin 160-40 mg compared with PRAVASINE 40 mg (p=0.019 and p=0.006 respectively). The TG level was significantly (p=0.001) more decreased by Fenofibrate/Pravastatin 160-40 mg (-22.6%) than with PRAVASINE 40 mg (-2.0%). The HDLc was significantly (p=0.009) more increased with Fenofibrate/Pravastatin 160-40 mg (+6.5%) compared with PRAVASINE 40 mg (+2.3%). The ratio ApoB/ApoA1, fibrinogen and hsCRP were significantly more reduced with Fenofibrate/Pravastatin 160-40 mg compared with PRAVASINE 40 mg (p<0.01). The percentage of patients achieving the therapeutic goals according to the NCEP ATP III at the end of the efficacy phase (Week 12) was significantly higher in the Fenofibrate/Pravastatin 160-40 mg group than in the PRAVASINE 40 mg group (19.2% versus 7.6% ; p = 0.008). The 10-year CHD risk was significantly (p<0.001) more decreased after 12 weeks with Fenofibrate/Pravastatin 160-40 mg (-27.4%; p < 0.0001) compared with PRAVASINE 40 mg (-7.6%; p = 0.041).			
Analysis description	**Safety results**			

	The safety profile evaluated with respect to the incidence of AEs and laboratory values was acceptable for all treatment groups during any analysis phase. During the 12-week efficacy phase, the incidence of AEs was similar in the Fenofibrate/Pravastatin 160-40 mg group (36.6%) compared to the PRAVASINE 40 mg group (32.0%). Twenty-five patients (10,1%) had AEs related to the study treatment: 13 patients with Fenofibrate/Pravastatin 160-40 mg and 12 patients with PRAVASINE 40 mg. Headache and muscle spasms were the most frequent drug-related AEs. The proportion of patients presenting an abnormal laboratory value at least once during the efficacy phase was significantly greater in the Fenofibrate/Pravastatin 160-40 mg group than in the PRAVASINE 40 mg group for creatinine ($p = 0.013$), creatinine clearance ($p = 0.044$) and ASAT ($p = 0.047$). No patient had an elevation of ASAT and/or ALAT > 3 UNL. Two patients in the PRAVASINE 40 mg group had an elevation of CPK > 3 UNL. Eleven patients (4.0%) were withdrawn from the study during the efficacy phase because of an AE (6 and 5 patients in the Fenofibrate/Pravastatin 160-40 mg and PRAVASINE 40 mg group respectively). Seven patients (2.8%) experienced SAEs: 5 patients (5 SAEs) in the Fenofibrate/Pravastatin 160-40 mg group and 2 patients (3 SAEs) in the PRAVASINE 40 mg group. Only 1 SAE (muscle pain) was considered as possibly related to Fenofibrate/Pravastatin 160-40 mg and led to discontinuation. In the follow-up report, the investigator modified the diagnosis from "muscle pain" to "rheumatic polymyalgia" and declared that the symptoms were probably not related to the study drug. During the 52-week safety phase, 274 AEs have been reported, of which 33 (12.0%) were related to Fenofibrate/Pravastatin 160-40 mg. Back pain and hypertension were the most frequent AEs. Transaminase increased, abdominal upper pain and nausea were the most frequent AEs related to the combination. Three patients had an elevation of ASAT and/or ALAT > 3 UNL. Three patients had an elevation of CPK > 3 UNL. Twelve patients (5.4%) experienced 19 SAEs. None of them were related to the study drug (Fenofibrate/Pravastatin 160-40 mg). Five patients (2.2%) were withdrawn from the study because of an AE. Neither myopathy nor rhabdomyolysis were reported during the study. No death was reported during the study. No clinically relevant differences in the laboratory values, vital signs, physical examination and ECG parameters were found between treatments during this study. The frequency of abnormal findings was comparable between treatments.
Analysis description	**Overall conclusions**
	The combination Fenofibrate/Pravastatin 160-40 mg in high risk patients with combined hyperlipidemia resulted in additional improvements in lipoprotein profile compared with PRAVASINE 40 mg monotherapy. The Fenofibrate/Pravastatin combination (160-40 mg per day) was well tolerated with a safety profile similar to PRAVASINE alone (40 mg per day). One year treatment with Fenofibrate/Pravastatin 160-40 mg did not raise any significant concern about the safety of the combination.

Analysis performed across trials (pooled analyses and meta-analysis)

Pooled efficacy data from the double blind cohort (SMB-FEPRA-0303 and Sc-PRAVA-06-02 studies) has been provided. The efficacy results are presented in table below as mean percentage changes from baseline to week 12.

Mean Percent Change for the double blind cohort (SMB-FEPRA-0303 and Sc-PRAVA-06-02)

Parameter Treatment	n	Baseline Mean (SD)	Week 12 Mean (SD)	% Change Mean (SD)	% LS mean (SE)	Treatment Differences LS Mean (SE) 95% CI p-value	
						FENO/ PRAVA vs. PRAVA	FENO/ PRAVA vs. FENO*
Non-HDL-C (mg/dl)							
FENO/PRAVA 160/40mg	358	165.8 (31.93)	147.4 (39.54)	-9.9 (22.11)	-10.5 (1.07)	-8.6 (1.69) (-11.9 , -5.3) <0.0001	-17.8 (2.15) (-22.1 , -13.6) <0.0001
PRAVA 40mg	230	173.9 (34.61)	166.9 (37.04)	-3.0 (16.61)	-1.8 (1.30)		
FENO 160mg	119	156.7 (29.30)	171.0 (40.60)	10.1 (21.48)	7.4 (1.98)		
LDL-C (mg/dl)							
FENO/PRAVA 160/40mg	358	133.7 (27.46)	124.4 (31.71)	-5.3 (22.84)	-6.6 (1.14)	-4.8 (1.79) (-8.3 , -1.3) 0.0071	-20.6 (2.28) (-25.1 , -16.2) <0.0001
PRAVA 40mg	230	137.6 (29.49)	132.1 (32.80)	-2.7 (19.75)	-1.8 (1.38)		
FENO 160mg	119	130.6 (27.29)	151.7 (35.33)	18.3 (25.35)	14.1 (2.10)		
HDL-C (mg/dl)							
FENO/ PRAVA 160/40mg	358	48.5 (9.63)	49.7 (11.27)	2.7 (14.16)	3.5 (0.72)	3.4 (1.13) (1.1 , 5.6) 0.0031	**-0.9 (1.45) (-3.8 , 1.9) 0.5290**
PRAVA 40mg	230	48.5 (9.46)	48.3 (9.98)	0.2(12.36)	0.1 (0.87)		
FENO 160mg	119	48.8 (8.99)	49.4 (9.57)	1.9 (13.77)	4.4 (1.34)		
TG (mg/dl)							
FENO/PRAVA 160/40mg	358	214.2 (89.18)	162.5 (99.08)	-19.9 (44.16)	-20.4 (2.16)	-26.3 (3.38) (-32.9 , -19.6) <0.0001	**-3.6 (4.32) (-12.1 , 4.9) 0.4034**
PRAVA 40mg	230	220.6 (85.94)	217.5 (84.31)	4.9 (40.21)	5.9 (2.60)		
FENO 160mg	119	199.6 (90.99)	162.4 (69.70)	-13.1 (33.40)	-16.8 (3.98)		

% Percentage Achieving NCEP ATP III Goals

Risk Category NCEP ATP III Goals	Treatment			
	FENO/ PRAVA 160/40mg (N = 358) n (%)	PRAVA 40 mg (N = 230) n (%)	FENO 160 mg (N = 119) n (%)	p-value**
LDL-C <100 mg/dL and non-HDL-C <130 mg/dL	68 (19.0)	20 (8.7)	5 (4.2)	<0.0001

Data were pooled from studies SMB-FEPRA-0303 and Sc-PRAVA-06-02. Baseline was defined as the last fasting measurement prior to the first dose of randomized study drug for Sc-PRAVA-06-02 and as the average of the 2 measurements prior to the first dose of randomized study medication for SMB-FEPRA-0303. Endpoint was defined as the last fasting measurement during the double-blind treatment period.
*p-value was obtained from the ANCOVA model with treatment and study as factors and baseline as a covariate for lipid parameters.
**p-value was obtained from Pearson's chi-square test for the percentage of patients achieving the goal.

The submitted results of the pooled analysis of the efficacy data from the double blind cohort SMB-FEPRA-0303 and Sc-PRAVA-06-02 studies are in line with those previously obtained in the individual studies. No significant information is derived from this analysis.

Clinical studies in special populations

No clinical studies in special populations were provided. Instead of, the applicant performed a *post hoc* pooled sensitivity analysis of SMB-FEPRA-0303 and Sc-PRAVA-06-02 during double-blind phases (that used the same comparator pravastatin 40mg). Subgroup analyses were performed to look for possible differences in treatment effect across groups. Analysis according to age and gender were performed.

Comparison of efficacy results in function of age: Pooled analyses have been performed on three sub-populations according to the age of patients i.e. < 65 years, 65 to 75 years and > 75 years. There are only 6 patients >75 years of age distributed among the 3 treatment groups in the double-blind cohort. As a consequence, the small size of this subgroup precludes meaningful interpretation of their lipid efficacy data and invalidates comparison with the other age subgroups. Therefore no summary is presented for this category of age. The efficacy results are presented in table below as mean percentage changes from baseline to week 12.

Mean Percent Change in function of age pooled analysis of SMB-FEPRA-0303 and Sc-PRAVA-06-02 studies

	< 65 years				≥ 65 years and ≤ 75 years			
Parameter Treatment	n	Baseline Mean (SD)	Week 12 Mean (SD)	% Change Mean (SD)	n	Baseline Mean (SD)	Week 12 Mean (SD)	% Change Mean (SD
Non-HDL								
FENO/PRAVA 160/40mg	290	163.9 (30.47)	146.3 (38.10)	-9.6 (21.75)	67	173.7 (36.69)	152.1 (45.40)	-11.3 (23.84)
PRAVA 40 mg	188	172.1 (36.12)	166.1 (37.95)	-2.5 (16.11)	37	181.3 (25.82)	170.2 (33.07)	-4.9 (19.62)
FENO 160 mg	98	157.3 (29.30)	170.9 (42.2)	9.4 (21.39)	21	154.1 (30.08)	171.7 (32.97)	13.2 (22.17)
LDL-C								
FENO/PRAVA 160/40mg	290	132.6 (27.04)	124.0 (30.24)	-4.8 (22.56)	67	138.0 (28.96)	126.0 (37.73)	-7.7 (24.19)
PRAVA 40 mg	188	(136.0 (30.58	131.2 (32.58)	-2.2 (18.86)	37	144.3 (23.40)	136.6 (35.06)	-4.0 (24.79)
FENO 160 mg	98	132.6 (28.42)	152.0 (36.82)	16.7 (24.89)	21	121.2 (19.13)	150.2 (28.06)	25.8 (26.76)
HDL-C								
FENO/PRAVA 160/40mg	290	48.2 (9.45)	290 49.1 (11.10)	2.0 (14.00)	67	49.7 (10.36)	52.3 (11.71)	5.7 (14.66)
PRAVA 40 mg	188	47.9 (9.37)	47.7 (9.97)	-0.03 (12.72)	37	51.08 (9.81)	51.5 (9.82)	1.5 (10.89)
FENO 160 mg	98	48.7 (8.65)	49.1 (9.32)	1.7 (13.64)	21	49.5 (10.62)	50.5 (10.84)	3.0 (14.67)
TG								
FENO/PRAVA 160/40mg	290	215.3 (91.69)	165.2 (103.21)	-18.5 (46.92)	67	209.6 (78.61)	151.6 (79.25)	-26.0 (29.31)
PRAVA 40 mg	188	221.8 (89.58)	218.6 (84.67)	5.5 (41.16)	37	215.3 (70.34)	214.7 (85.18)	2.6 (35.69)
FENO 160 mg	98	190.3 (80.38)	162.9 (73.38)	-10.2 (34.35)	21	242.6 (123.09)	159.7 (50.41)	-26.5 (25.03)

In total, 576 patients (81.5%) were younger than 65 years old, 125 patients (17.7%) were between 65 and 75 years old and only 6 patients (0.8%) were older than 75 years old. The magnitude of the mean percent changes in non-HDL-C, LDL-C, and TG appeared to be slightly greater in the ≥65 to ≤75 years of age subgroup than in the <65 years of age subgroup for each treatment group and in the Pravafenix arm. For HDL-C, the mean change is similar between the 2 subgroups of treatments. However, the CHMP acknowledged the limitation of such post-hoc pooled analyses, particularly in terms of the power, since the number of patients in each subgroup is very limited.

Comparison of efficacy results in function of gender: The study populations were adequately balanced for gender: 386 patients (54.6%) were male and 321 patients (45.4%) were female. Overall, the mean percent change in non-HDL-C versus baseline observed with Pravafenix is similar in men (-9.3 + 19.1%) and in women (-10.7 + 25.4%). The magnitude and direction of the mean percent changes in TG were also similar for male (-20.8 + 37.19) and female (-18.7 + 51.69) patients in the Pravafenix 160/40 mg treatment group. However, the magnitude of the mean percent changes in LDL-C (-7.9% vs -3.2%, respectively) and HDL-C (4.2% vs 1.5%, respectively) appeared to be greater in female than male patients in the Pravafenix 160/40 mg treatment group.

Supportive study(ies)

Sc-PRAVA-06-02: Multi-center, prospective, longitudinal, randomized, double-blind, phase III Study to evaluate the efficacy and safety of daily administration of Pravastatin 40mg or fenofibrate 160mg or Pravafen (the combination of pravastatin and fenofibrate 40/160mg) for 12 weeks, followed by a 52-week open-label safety phase of Pravafen alone, in the treatment of combined hyperlipidemia. The primary objective of the study is to evaluate the efficacy of administering either Pravastatin 40mg or Fenofibrate 160mg or Pravafen (the combination of Pravastatin and Fenofibrate 40/160mg) daily for 12 weeks, followed by a Pravafen open-label 52-week safety follow-up, in the treatment of combined hyperlipidemia. The secondary objective was a safety comparison over 12 weeks and long-term safety assessment over 52 weeks.
The results of the Efficacy Phase of the present study confirm the findings of these studies describing the synergistic therapeutic benefits of specific statin-fibrate combinations: Non-HDL cholesterol is more effectively reduced by combination Pravafen (-7.0%) than either monotherapy pravastatin (+2.8%) or monotherapy fenofibrate (+10.4%). LDL Cholesterol is reduced by combination therapy with Pravafen (-1.1%) and increased with monotherapy pravastatin (+3.8%) and fenofibrate (19.0%). Triglycerides are more effectively reduced by Pravafen (-19.5%) than either monotherapy pravastatin (+12.8%) or monotherapy fenofibrate (-13.4%).

FENOPRA-III-05-01: This was a Phase III, multicenter, open-label study to evaluate the safety of Pravafenix 160/40mg administered once daily for 24 weeks in high cardiovascular risk patients with mixed dyslipidemia. More extensive information regarding design, population, outcomes and statistical analysis are provided in the different sections of this report. The primary efficacy parameter was the mean percent change in non-HDL-C from baseline (recorded at the baseline laboratory exam) to Week 24/end of study. Secondary efficacy parameters included change from baseline to Week 24/end of study in LDL-C, HDL-C, TG, TC, Apo A_1, Apo B, Apo B/Apo A_1, hsCRP, and fibrinogen values. The results are in line with those obtained in the main studies. Safety data from this study have been included in the safety database for Pravafenix.

2.5.3. Discussion on clinical efficacy

During the first part of the scientific evaluation of the Pravafenix MAA the CHMP considered that the submitted data were not sully supportive to sustain the benefit of this FDC. Despite biological effects observed in the submitted clinical studies, the benefit of Pravafenix assessed on lipid parameters and responder's rate was uncertain. Considering the expected pattern for respective classes of these drugs, results have shown a more potent effect of fenofibrate on TG and HDL-C while pravastatin is superior in reducing total cholesterol and LDL-C. In the overall clinical programme, the combination mainly showed a decrease in TG with an incremental increase in HDL-C and in some cases further reduction on total cholesterol and LDL-C. If significant, results on LDL-C are very limited.

In that context, publication of ACCORD (Action to Control Cardiovascular Risk in Diabetes) study results of in March 2010, which studied long term efficacy and safety use of a combination of a statin (simvastatin) and fenofibrate on cardiovascular endpoints, was considered essential to resolve some of these issues. Results of the ACCORD study were also believed to be useful when considering the limited database presented for Pravafenix. Therefore, the CHMP requested an analysis of the results of ACCORD study in order to help solve the major issues raised for the Pravafenix dossier before a definite assessment of the benefit risk of this new fixed dose combination can be made.

Thus, the following considerations have been evaluated during the assessment:

- Review of the overall results of ACCORD study focusing on the effects of the addition of fenofibrate in patients inadequately controlled by simvastatin monotherapy as studied in this trial.
- Analysis of the subgroup of patients with atherogenic dyslipidemia (TG$\geq$204 mg/dL and HDL$\leq$34 mg/dL, potentially benefiting from a statin/fenofibrate combination according to results of the ACCORD study. Additional new subgroup analysis of patients with atherogenic dyslipidemia in study SMB-FEPRA-0303 and from data published in the literature.
- Justification of the claimed of equipotency between statins (other statins doses equivalent to pravastatin 40 mg).

Effect on lipid parameters

Expected results observed in the initial clinical dossier of Pravafenix have shown a more potent effect of fenofibrate on TG and HDL-C, while pravastatin is superior in reducing total cholesterol and LDL-C.

In the overall clinical programme, the combination mainly showed a decrease in TG with an incremental increase in HDL-C and in some cases further reduction on total cholesterol and LDL-C.

These results are in line with results obtained in the ACCORD study, in a selected population of type 2 diabetic patients. In this subgroup, biological effects of the addition of fenofibrate to simvastatin are better compared to other included patients. However, despite biological effects observed in the submitted clinical studies, the benefit of Pravafenix assessed on lipid parameters, especially on LDL-C, and responder's rate is somewhat limited.

Additional subgroup post hoc analyses from the study SMB-FEPRA-0303.

To further sustain efficacy results of Pravafenix in the originally claimed indication, two additional post hoc analyses from clinical study SMB-FEPRA-0303 were provided. The aim of both analysis was to compare the effects of Pravafenix on lipid parameters, using the same definitions of lipid abnormalities as in the ACCORD study: i) in patients with only low baseline HDL-C (<40mg/dL for men and <50mg/dL for women); ii) and in patients with both TG value >200mg/dL and low HDL value (<40mg/dL for men and <50mg/dL for women) at baseline.

From the provided analysis, it was shown that the effect of Pravafenix versus pravastatin on non HDL-C and LDL-C appears to be more pronounced in patients with low HDL at baseline than in patients with normal HDL-values. Furthermore, this effect also appears more pronounced in patients with high TG and low HDL at baseline as defined above. However, these subgroups only concern a small number of patients, i.e. 70 patients (29.3%) with only low HDL-C at baseline and 49 patients (25.7%) who met criteria for TG and HDL, and are thus limited to represent the general population. In addition, from a methodological point of view, as usual post-hoc analyses must be taken with cautious. Overall, the strength of evidence is limited, due to small number of patients to support an indication of Pravafenix in all dyslipidemic patients. Therefore, positive biological effect on the pravastatin/fenofibrate combination, sustained by sufficient data, could be endorsed only in patients with high TG and low HDL-C. Lastly, post-analyses only showed effects on lipid parameters but not on CV morbidity or mortality due to the limited duration of studies. This was considered an importance issue as patients with dyslipidaemia, i.e. mainly diabetics should be long term treated.

In order to identify which population could benefit from a simvastatin/fenofibrate combination in reducing cardiovascular events in the ACCORD study and whether these results can be extrapolated to Pravafenix, the following has been taken into account:

Main results of the ACCORD study

In this study, 5518 patients with type 2 diabetes (mean age : 62.3 years; 30.7% women), who were at high risk for cardiovascular disease (36.5% with prior CV events) received either fenofibrate (160 mg or equivalent dose) or matching placebo in addition to open label simvastatin 20 to 40mg. The primary outcome was the first occurrence of non fatal myocardial infarction (MI), non fatal stroke, or death from cardiovascular causes. The mean follow-up was five years until death or the final visit that took place in early 2009. Eight percent reduction in the primary endpoint with combination of pravastatin and fenofibrate did not reach statistical significance (p=0.32). The combination of fenofibrate and simvastatin in diabetic patients inadequately controlled by simvastatin alone did not reduce the rate of fatal cardiovascular events, non fatal MI, or nonfatal stroke; as compared to simvastatin alone. According to the authors themselves, these results do not support the use of combination therapy with fenofibrate and simvastatin to reduce cardiovascular risk in the majority of high risk patients with type 2 diabetes. Thus, the long term benefit on cardiovascular events of the addition of fenofibrate to patients inadequately controlled by a statin (simvastatin) monotherapy is not established on the basis of the ACCORD study in the overall type 2 diabetic patients presenting dyslipidaemia.

However, a specific sub-groups analysis identified a specific population, i.e. patients with hyperlipidaemia defined by high TG levels >204 mg/dL and low HDH values <34 mg/dL, where benefit on lipid parameters, but also on cardiovascular events, was observed contrary to the overall population. Results on the primary outcome rate were 12.4% in the fenofibrate/simvastatin group versus 7.3% in the simvastatin monotherapy group whereas such rates were 10.1% in both study groups for all other patients.

Certainties and uncertainties of the ACCORD study and possibility of extrapolation of the results of the this study to Pravafenix

ACCORD population: Patients included in the ACCORD study were exclusively diabetics, of which the majority did not present mixed dyslipidaemia. Less than 20% of patients had simultaneous high TG and low HDL-C levels. Indeed, no minimal TG value was specified; the mean baseline TG level was 162mg/dL. In addition, almost 40% of the patients included in the study were not receiving statin at baseline prior to enrolment. Thus, the ACCORD study population was quite different from the population that was studied in the Pravafenix clinical development programme.

Clinical efficacy: Regardless of whether efficacy on lipid parameters is demonstrated in this study in the overall population, as previously stated, it appears evident that ACCORD results on hard endpoints do not support the routine use of the combination therapy with fenofibrate and simvastatin in reducing cardiovascular events in overall high risk patients with type 2 diabetes presenting dyslipidaemia. In addition, a pre-specified subgroup analysis based on gender identified a statistically significant treatment-by-gender interaction ($p = 0.01$). The increased risk for major cardiovascular events (9%) for fenofibrate/simvastatin combination compared to 6% for simvastatin alone for women evaluated in this study is of concern. Moreover, results on the composite secondary endpoint, major coronary disease event, non fatal stroke, non fatal MI, also showed a tendency to be increased, although not significantly. In that context, uncertainties remain about whether the overall beneficial effect is robust enough to support an indication of a statin/fenofibrate combination in patients with mixed hyperlipidaemia (defined by high TG and low HDL levels) and high CV risk, inadequately controlled by a statin monotherapy, based only on data from the ACCORD publication. This concern could also apply to the current Pravafenix dossier where, in addition to the effects on lipid parameters, effects on cardiovascular endpoints in long term use are not entirely demonstrated.

This concern has been extensively discussed during the benefit/risks reassessment on fibrates (including fenofibrate) through Art 31 referral procedure.

Overall, the CHMP concluded that Pravafenix would be a beneficial treatment options for a substantial portion of patients at high CV risk, particular those with elevated TG and low HDL-C despite a 40mg pravastatin therapy. The outcome of this referral evaluation has a direct impact on the Pravafenix assessment.

Equipotency of statins

Regarding the original claim on statin equipotency, the CHMP was of the opinion that the presented data do not support the use of Pravafenix following any type of statin; only an indication following optimal dose of pravastatin could be accepted. This is mainly due to the lower potency of pravastatin as compared to the more frequently used statins (i.e. simvastatin, atorvastatin and rosuvastatin). Moreover, as individual response is not the same as population level response, in real practice there is no reason for switching patients controlled by one statin to Pravafenix.

Moreover, several previously conducted clinical trials have shown that the efficacy of statins is dose-dependent. Thus, it is possible that in ACCORD trial, simvastatin might not have used at the most effective dose and the results with an addition of fenofibrate to a full simvastatin dose are therefore unknown. It remains questionable whether the results of ACCORD study in this aspect are transferable to Pravafenix and only the second line indication limited to the use of pravastatin 40mg can be approvable.

The applicant requested an Oral Explanation for the discussion of the indication and the equipotency of statins, however in line with the above arguments, clinical results and the outcome of Article 31 referral on fibrates concluded during the assessment of Pravafenix, the following indication has been considered approvable by the CHMP:

"Pravafenix is indicated for the treatment of high CHD-risk adult patients with mixed dyslipidaemia characterised by high triglycerides and low HDL-cholesterol levels whose LDL-C levels are adequately controlled while on a treatment with pravastatin 40 mg monotherapy."

2.5.4. Conclusions on the clinical efficacy

An Oral Explanation on the discussion of the indication of Pravafenix and the equipotency of statins was conducted, however, in line with the above arguments, clinical results and the outcome of Article 31 referral on fibrates finalised during the assessment of Pravafenix, the following indication has been considered approvable by the CHMP:

"Pravafenix is indicated for the treatment of high CHD-risk adult patients with mixed dyslipidaemia characterised by high triglycerides and low HDL-cholesterol levels whose LDL-C levels are adequately controlled while on a treatment with pravastatin 40 mg monotherapy."

2.6. Clinical safety

Safety data were derived from four phase III clinical trials. Three of them were double-blind randomised studies.

Study SMB-FEPRA-0303 compared the efficacy on 12 weeks of fenofibrate/pravastatin 160/40 mg FDC, versus pravastatin 40 mg in high CHD risk patients with mixed hyperlipidemia (n=248 patients included in the safety analysis). After this 12-week efficacy phase, all patients received FDC during an open safety phase of 52 additional weeks (n=224 patients included in the safety analysis).

Study FENOPRA-III-06-1 compared the efficacy on 12 weeks of FDC versus simvastatin 20 mg (with or without open-label administration of ezetimibe) in type 2 diabetic patients with mixed hyperlipidemia, at high CHD risk (n=291 patients included in the safety analysis) or very high CHD risk (n=272 patients included in the safety analysis). After this 12-week efficacy phase, all patients received FDC with or without ezetimibe during an open safety phase of 12 additional weeks (n=537 patients included in the safety analysis, of which 281 were in the high CHD risk and 256 in the very high CHD risk).

Study Sc-PRAVA-06-02 compared the efficacy of 12 week treatment with FDC versus pravastatin 40 mg versus fenofibrate 160 mg in patients with mixed hyperlipidemia (n=563 patients included in the safety analysis; 240 patients in FDC, 113 in pravastatin, 122 in fenofibrate). After this 12 week efficacy phase, all patients received FDC during an open safety phase of 52 additional weeks (n=386).

FENOPRA-III-05-1 was an open label study and focused on safety aspect of FDC in high or very high CHD risk patients with mixed hyperlipidemia treated for 24 weeks (n=342 patients included in the safety analysis).

Patient exposure

Patients analysed in the pooled analysis are patients from the safety populations of each of the individual studies; i.e. randomised patients who took at least one dose of the study drug. Data from these patients were pooled in two different analysis cohorts:

- The "double-blind cohort" including all patients from the 12-week double-blind phases of studies SMB-FEPRA-0303, Sc-PRAVA-06-02, FENOPRA-III-06-1 to compare the extent of safety issues for the combination versus a statin monotherapy (pravastatin 40 mg in the SMB-FEPRA-0303 and Sc-PRAVA-06-02 studies or simvastatin 20 mg in the FENOPRA-III-06-1 study) and fenofibrate 160 mg (in the Sc-PRAVA-06-02 study).
- The "all studies cohort" combining the data from the 4 phase III trials: SMB-FEPRA-0303, Sc-PRAVA-06-02, FENOPRA-III-06-1 and FENOPRA III-05-1. This analysis was conducted over the entire study period (from week 0 until the end of the study, when patients are treated with Pravafenix 160/40 mg). Thus, this database includes all patients having taken at least one dose of Pravafenix at any time during any phase III clinical trial. This database allows an assessment of the long-term safety profile of Pravafenix.

The summary of patient exposure from these analyses is given in the tables below. A total of 1566 patient were exposed to at least one dose of Pravafenix, 928 patients were exposed for 24 weeks and 395 patients were exposed for 1 year. These patient exposures can be considered acceptable for safety evaluation.

Overview of cumulative exposure - double-blind cohort

Cumulative exposure	Feno/Prava N=645		Statin* N=519		Fenofibrate N=122	
	N	%	N	%	N	%
at least 1 day	645	100.00	519	100.00	122	100.00
at least 1 week	641	99.38	512	98.65	122	100.00
at least 4 weeks	631	97.83	505	97.30	118	96.72
at least 12 weeks	401	62.17	362	69.75	40	32.79
Feno/Prava= FDC fenofibrate/pravastatin 160/40 mg * Statin: Pravastatin 40 mg or Simvastatin 20 mg depending on the study from which the data are issued.						

Overview of cumulative exposure - all studies cohort

Cumulative exposure	Feno/Prava N=1566	
	N	%
at least 1 day	1566	100.00
at least 1 week	1556	99.36
at least 4 weeks	1540	98.34
at least 12 weeks	1388	88.63
at least 24 weeks	928	59.26
at least 52 weeks	395	25.22
at least 64 weeks	148	9.45
Feno/Prava= FDC fenofibrate/pravastatin 160/40 mg		

Adverse events

Double-blind safety cohort

The below table provides an overview of adverse events for the double-blind cohort. In total, 453 (35.23%) patients had a Treatment Emergent Adverse Event (TEAE). Across the treatment groups, the percentage of patients with a TEAE in the double-blind cohort was of 35.97% for Pravafenix, 28.71% for statin and 59.02% for fenofibrate group. In total, 151 (11.74%) patients had a drug-related TEAE. Across the treatment groups, the percentage of patients with a drug-related TEAE was 12.25%, 8.86% and 21.31% for Pravafenix, statin and fenofibrate group, respectively. Across all treatment groups, most TEAEs and drug-related TEAEs were considered mild or moderate in intensity.

Overview of Adverse Events - double-blind cohort

Categories	Feno/Prava	Statin*	Feno	Total
	N=645	N=519	N=122	N=1286
One or more TEAEs	232 (35.97%)	149 (28.71%)	72 (59.02%)	453 (35.23)
Drug-related TEAEs	79 (12.25%)	46 (8.86%)	26 (21.31%)	151 (11.74)
*Intensity of TEAEs***				
Mild	145 (22.48%)	103 (19.85%)	41 (33.61%)	289 (22.47)
Moderate	118 (18.29%)	70 (13.49%)	51 (41.80%)	239 (18.58)
Severe	23 (3.57%)	9 (1.73%)	3 (2.46%)	35 (2.72)
*Intensity of drug-related TEAEs***				
Mild	48 (7.44%)	31 (5.97%)	18 (14.75%)	97 (7.54)
Moderate	35 (5.43%)	18 (3.47%)	11 (9.02%)	64 (4.98)
Severe	7 (1.09%)	2 (0.39%)	0 (0.00%)	9 (0.70)
Death	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00)
SAE	11 (1.71%)	4 (0.77%)	0 (0.00%)	15 (1.17)
Drug-related SAE	3 (0.47%)	0 (0.00%)	0 (0.00%)	3 (0.23)
Discontinuation due to AE	33 (5.12%)	14 (2.70%)	6 (4.92%)	53 (4.12)
Discontinuation due to drug-related AE	19 (2.95%)	9 (1.73%)	6 (4.92%)	34 (2.64)

Feno/Prava=FDC fenofibrate/pravastatin,160-40mg, SAE=Serious Adverse Event, TEAE=Treatment Emergent Adverse Event.
* Statin: Pravastatin 40 mg or Simvastatin 20 mg depending on the study from which the data are issued.
** A patient can be reported once in each intensity category

No patients died during the double-blind period of the 3 phase III studies. In total, 15 (1.17%) patients had an SAE during the double-blind period: 11 (1.71%) patients in Pravafenix group, 4 (0.77%) in the statin group and none in the fenofibrate group. Three patients had SAEs that were considered to be related to the study medication, all in the Pravafenix group: polymyalgia rheumatica (SMB-FEPRA-0303), abdominal pain and cholecystectomy (Sc-PRAVA-06-02) and gastrointestinal haemorrhage and anaemia (FENOPRA-III-06-1).

Discontinuation: In total, 53 (4.12%) patients discontinued the study during the double-blind period due to an AE. The Pravafenix group (33 patients, 5.12%) had a higher percentage of patients who discontinued from the study due to an adverse event compared to the statin group (14 patients, 2.70%). Nineteen patients (2.95%) in the Pravafenix and 9 patients (1.73%) in the statin group discontinued the study due to a drug-related AE.

Most frequent AEs: The numbers of patients with for the most frequent TEAEs by system organ class, preferred term (≥1% in any treatment group) and related to the treatment are summarised in the following tables. Overall, the most common TEAEs experienced by patients occurred in the system organ classes of musculoskeletal and connective tissue disorders, gastrointestinal disorders, infections and infestations and investigations. The most frequent AEs observed with Pravafenix were arthralgia, nausea and cough. In the statin group, the most common adverse events were diarrhoea, headache and back pain; and in the fenofibrate group, these were nasopharyngitis, pain in extremity and headache. The incidence of those adverse events was generally low and no significant difference in frequency was observed between the fixed dose combination group and the monotherapies. No new adverse events were identified for any of the treatments.

Most frequent TEAEs (> 1% in any treatment group), double-blind cohort

Body system	PT name	Feno/ Prava	Statin*	Feno
		N=645	N=519	N=122
Gastrointestinal disorders	Abdominal pain	6 (0.93%)	1 (0.19%)	2 (1.64%)
	Abdominal pain upper	7 (1.09%)	6 (1.16%)	1 (0.82%)
	Constipation	7 (1.09%)	4 (0.77%)	3 (2.46%)
	Diarrhoea	7 (1.09%)	11 (2.12%)	2 (1.64%)
	Gastrooesophageal reflux disease	4 (0.62%)	1 (0.19%)	2 (1.64%)
	Nausea	14 (2.17%)	5 (0.96%)	1 (0.82%)
	Toothache	2 (0.31%)	1 (0.19%)	2 (1.64%)
General disorders and administration site	Fatigue	4 (0.62%)	3 (0.58%)	2 (1.64%)
	Oedema peripheral	5 (0.78%)	1 (0.19%)	2 (1.64%)
Infections and infestations	Bronchitis	10 (1.55%)	6 (1.16%)	3 (2.46%)
	Nasopharyngitis	8 (1.24%)	4 (0.77%)	7 (5.74%)
	Sinusitis	11 (1.71%)	4 (0.77%)	2 (1.64%)
	Upper respiratory tract infection	7 (1.09%)	2 (0.39%)	4 (3.28%)
	Urinary tract infection	3 (0.47%)	3 (0.58%)	2 (1.64%)
Investigations	Apolipoprotein B increased	1 (0.16%)	4 (0.77%)	2 (1.64%)
	Blood cholesterol increased	2 (0.31%)	1 (0.19%)	4 (3.28%)
	Blood creatine phosphokinase increased	7 (1.09%)	4 (0.77%)	4 (3.28%)
	Blood Creatinine increased**	3 (0.47%)	1 (0.19%)	1 (0.82%)
	Creatinine renal clearance decreased***	11 (1.71%)	3 (0.58%)	1 (0.82%)
	Low density lipoprotein increased	4 (0.62%)	1 (0.19%)	3 (2.46%)
	Transaminases increased****	6 (0.93%)	0 (0.00%)	4 (3.28%)
Musculoskeletal and connective tissue disorders	Arthralgia	15 (2.33%)	4 (0.77%)	4 (3.28%)
	Back pain	5 (0.78%)	7 (1.35%)	4 (3.28%)
	Muscle spasms	7 (1.09%)	4 (0.77%)	3 (2.46%)
	Musculoskeletal pain	8 (1.24%)	4 (0.77%)	1 (0.82%)
	Myalgia	3 (0.47%)	6 (1.16%)	2 (1.64%)
	Pain in extremity	7 (1.09%)	7 (1.35%)	5 (4.10%)
Nervous system disorders	Headache	8 (1.24%)	10 (1.93%)	5 (4.10%)
Renal and urinary disorders	Renal insufficiency	1 (0.16%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders	Cough	11 (1.71%)	3 (0.58%)	3 (2.46%)
	Sinus congestion	5 (0.78%)	0 (0.00%)	2 (1.64%)
Skin and subcutaneous tissue disorders	Rash	5 (0.78%)	2 (0.39%)	2 (1.64%)
Vascular disorders	Hypertension	4 (0.62%)	6 (1.16%)	3 (2.46%)

Feno/Prava= FDC fenofibrate/pravastatin 160/40 mg, PT=Preferred Term.
*Statin: Pravastatin 40 mg or Simvastatin 20 mg depending on the study from which the data are issued.
**Blood creatinine increased includes PT blood creatinine increased, blood creatine increased, blood creatinine abnormal
***Creatinine renal clearance decreased includes glomerular filtration rate decreased and creatinine (renal) clearance decreased
****Transaminases increased includes ALAT increased, ASAT increased and transminase(s) increased
Any event with occurrence over 1% in any treatment group is reported.

Most frequent TEAEs related to the treatment (> 1% in any treatment group), double-blind cohort

Body system	PT name	Feno/ Prava	Statin*	Feno

		Feno/ Prava	Statin*	Feno
		N=645	N=519	N=122
Gastrointestinal disorders	Constipation	7 (1.09%)	2 (0.39%)	2 (1.64%)
	Diarrhoea	5 (0.78%)	8 (1.54%)	0 (0.00%)
Investigations	Blood creatine phosphokinase increased	3 (0.47%)	2 (0.39%)	3 (2.46%)
	Transaminases increased**	3 (0.47%)	0 (0.00%)	2 (1.64%)
Musculoskeletal and connective tissue disorders	Myalgia	2 (0.31%)	6 (1.16%)	0 (0.00%)
	Pain in extremity	3 (0.47%)	2 (0.39%)	2 (1.64%)
Nervous system disorders	Headache	4 (0.62%)	4 (0.77%)	2 (1.64%)
Feno/Prava= Fixed-dose combination fenofibrate/pravastatin 160/40 mg, PT=Preferred Term. * Statin: Pravastatin 40 mg or Simvastatin 20 mg depending on the study from which the data are issued. **Transaminases increased includes ALAT increased, ASAT increased and transminase(s) increased. Any event with occurrence over 1% in any treatment group is reported.				

All studies cohort (up to 64 weeks)

In total, 684 (43.68%) patients had a TEAE, and 190 (12.13%) patients had a TEAE that was considered related to study medication by the investigators. Sixty-four (4.09%) patients had a SAE. In 3 (0.19%) cases, the SAEs were considered to be related to the study medication. These cases are those detailed for the double-blind cohort.

Discontinuation: In total, 97 (6.19%) patients were discontinued due to a TEAE and 54 (3.45%) patients discontinued due to a drug-related TEAE.

Overview of Adverse Events - all studies cohort

Categories	Feno/ Prava
	N=1566
One or more TEAEs	684 (43.68%)
Drug-related TEAEs	190 (12.13%)
Intensity of TEAEs*	
Mild	435 (27.78%)
Moderate	419 (26.76%)
Severe	88 (5.62%)
Intensity of drug-related TEAEs*	
Mild	109 (6.96%)
Moderate	98 (6.26%)
Severe	18 (1.15%)
Death**	2 (0.13%)
SAE	64 (4.09%)
Drug-related SAE	3 (0.19%)
Discontinuation due to AE	97 (6.19%)
Discontinuation due to drug-related AE	54 (3.45%)
Feno/Prava= FDC fenofibrate/pravastatin 160/40 mg, SAE=Serious Adverse events, TEAE=Treatment emergent adverse events. *A patient can be reported once in each intensity category ** One death was not included in the database	

Most frequent AEs: The numbers of patients with for the most frequent TEAEs by system organ class and preferred term (≥1% in any treatment group) for the all studies cohort following up to 64 weeks of treatment with PRAVAFENIX 160/40 mg are summarised in the table below. The system organ classes with the greatest number of TEAEs were infections and infestations, musculoskeletal and connective tissue disorders, gastrointestinal disorders and investigations. The most frequent TEAEs were back pain, hypertension, decreased creatinine renal clearance and bronchitis. Increased levels of transaminases were the only AE related to the study drug observed in more than 1% of the patients.

Most frequent TEAEs (> 1%), all studies cohort

Body system	PT name	Feno/ Prava N=1566
Gastrointestinal disorders	Abdominal pain upper	20 (1.28%)
	Constipation	21 (1.34%)
	Diarrhoea	21 (1.34%)
	Dyspepsia	16 (1.02%)
	Nausea	34 (2.17%)
Infections and infestations	Bronchitis	37 (2.36%)
	Influenza	18 (1.15%)
	Nasopharyngitis	29 (1.85%)
	Sinusitis	31 (1.98%)
	Upper respiratory tract infection	29 (1.85%)
	Urinary tract infection	17 (1.09%)
Investigations	Blood creatine phosphokinase increased	25 (1.60%)
	Blood creatinine increased*	18 (1.15%)
	Creatinine renal clearance decreased**	38 (2.43%)
	Transaminases increased***	22 (1.40%)
Musculoskeletal and connective tissue disorders	Arthralgia	32 (2.04%)
	Back pain	44 (2.81%)
	Muscle spasms	23 (1.47%)
	Musculoskeletal pain	18 (1.15%)
	Myalgia	20 (1.28%)
	Pain in extremity	30 (1.92%)
Nervous system disorders	Headache	19 (1.21%)
Respiratory, thoracic and mediastinal disorders	Cough	28 (1.79%)
Vascular disorders	Hypertension	42 (2.68%)

Feno/Prava= FDC fenofibrate/pravastatin 160/40 mg, PT=Preferred Term.
*Blood creatinine increased includes PT blood creatinine increased, blood creatine increased, blood creatinine abnormal
**Creatinine renal clearance decreased includes glomerular filtration rate decreased and creatinine (renal) clearance decreased
***Transaminases increased includes ALAT increased, ASAT increased and transminase(s) increased

Serious adverse event/deaths/other significant events

Deaths

Fatal outcome was reported in 3 patients, of which two were in the FDC group (Sc PRAVA 06-02 and FENOPRA III-05-1) and one in simvastatin+ezetimibe group (FENOPRA III-06-1). All patients have been diagnosed with a cancer and died after study discontinuation. The cause of death was related to cancer in two cases and to acute coronary syndrome in one case.

Serious adverse events other than death

Efficacy phase: Serious adverse events (SAEs) were reported in statins (0.8%) and FDC (1.7%) groups. No SAE was reported in fenofibrate group. Only some SAEs were considered related to the treatment and were reported in the FDC group: polymyalgia rheumatica, abdominal pain and cholecystectomy due to cholelithiasis, gastrointestinal haemorrhage with subsequent anaemia.

Safety phase: More patients experienced SAEs during the safety phase when compared with the efficacy phase (3.6% vs 1.7%), of which none was related to the treatment.

Observed SAEs were mostly related to cardiac events (myocardial infarction, coronary arterial disease, arrhythmia, cardiac failure), mainly in high CV risk patients, to neoplasms (breast cancer, bronchial carcinoma, lymphoma, lung neoplasm, ovarian cancer, prostate cancer, melanoma) and to surgical and medical procedures. All these SAEs were unrelated to study drug.

Acute pancreatitis was reported in two patients and was considered unrelated to treatment. In one case, the event led to patient's discontinuation. In the other case, the patient recovered without discontinuation of the study drug. Two other cases of pancreatitis have been reported but were considered as non serious.

Pulmonary embolism was reported in two patients and was considered unrelated. In one case, the study drug was temporarily discontinued and the patient recovered. In the other case, the patient

presented a pulmonary embolism secondary to deep venous thrombosis after patella fracture and incompletely recovered without modification of the treatment. Two TIA and one stroke were also noted during this period; all were considered unrelated.

Laboratory findings

Creatine phosphokinase (CPK)

Efficacy phase: Overall, increase of CPK was reported in all studies and in all treatment groups. This increase varied between 22% and 40%. The mean observed CPK increase was higher in the statin group (+26%) than in the FDC (+10.6%) and fenofibrate group (+15%). The majority of patients experienced increase of CPK (<5UNL). Only few patients reported CPK between 3-5UNL in all treatment groups: 1.6% in FDC, 1% in statins and 0.8% in fenofibrate. Only three patients in statin group (0.6%) and 2 in fenofibrate (1.6%) experienced CPK increase between 5-10 UNL. No muscular symptoms were associated with the increase of CPK except in one patient in statin group who experienced an increase over 10UNL associated with muscular symptom.

Safety phase: The increase of CPK was more frequently reported during the safety phase, approximately 40% of patients had an increase <5UNL. In one study, the increase of CPK was reported in additional 20% of patients. As in efficacy phase, the percentage of patients with increased CPK between 3-5 UNL remains stable. A total of 0.4% of patients experienced increased CPK 5-10 UNL *vs* none during the efficacy phase.

Alanine aminotransferase/Aspartate aminotransferase (ALT/AST)

Efficacy phase: Increase of AST/ALT was reported in all treatment groups and was more frequent in the FDC group. This increase varied between 20% and 40%. The majority of patients experienced moderate increase of AST/ALT (≤3UNL). However no separate data was provided for ALT and AST increase except for one study, although increased ALT is more indicative of hepatic toxicity (if AST increase is noted, data regarding alkaline phosphatase and conjugated bilirubin should be provided in order to attribute the AST increase to liver damage). These data were provided only for one study (FENOPRA III-06-1). The increase of ALT and AST between 3-5 UNL was similar in FDC and statin groups and was reported in only one patient each (0.16% and 0.19% respectively) and in two patients in fenofibrate group (1.64%). Two patients experienced both increase of ALT and AST>5 UNL with the FDC and one patient reported increase AST >5 UNL in the statins group.

Safety phase: The increase of AST and ALT was reported for approximately 20 to 40% of patients and the majority of patients experienced moderate increase <3UNL. The increase of ALT between 3-5UNL was slightly more frequent than in the efficacy phase (0.6% *vs* 0.16% respectively). Similar finding was reported for increase ALT >5UNL (0.3% *vs* 0.16% respectively). The increase of AST levels between 3-5 UNL was similar to the efficacy phase as was the increase of AST levels >5UNL.

Blood Creatinine clearance (CrCl) and creatinine

Efficacy phase: The provided data are to be interpreted with caution since the proposed stratification is not in line with the Kidney Disease Outcomes Quality Initiative (K/DOQI) classification. The frequency of patients with a ClCr<60 ml/min increased in FDC (from 4.5% at baseline to 10.7%) and in fenofibrate (from 0.8% to 2.5%) groups. This was not observed in the statin group (4.4% to 3.5%).

Safety phase: The frequency of patients in FDC group with a ClCr<60 ml/min was similar to the frequency observed during the efficacy phase (10% vs 10.7%). The frequency of creatininemia >20 mg/l increased to 1.1% during the safety period versus 0.5% during the efficacy period.

Homocysteine

Homocysteine levels were only collected in the four arm of study FENOPRA-III-06-1. During the efficacy period, homocysteine level remained unchanged in simvastatin group, associated or not with ezetimibe, but a statistical significant increase was reported in the FDC group. The between groups difference was statistically significant in both strata. Statistically significant increases were also reported during the safety period in both strata (25.0±51.2% in the high CV risk and 20.6±41.6% in the very high CV risk).

Vital signs and ECG

There were no clinical meaningful changes in diastolic, systolic blood pressure or heart rate in any group during the whole study. Additionally, no clinical relevant change in body weight was noted in FDC or statin groups (data not available for fenofibrate) during the efficacy phase and under FDC during the safety phase.

Safety in special populations

Subgroup analysis in the different individual studies was not performed. However, subgroup analyses were performed on pooled data of patients receiving at least one dose of Pravafenix. Following analyses were conducted:

- Diabetic patients (55% of the global population),
- Age: <65 years (77.6%), 65 to 75 years (19.8%) and >75 years (2.6%),
- Gender: 55.5% male, 44.5% female,
- BMI: 18-25 kg/m^2 (7.5%), 25-30 kg/m^2 (39.4%) and >30 kg/m^2 (53%),
- Renal status: clearance <60 ml/min (6%), between 60-75 ml/min (14.4%) and >75 ml/min (79.6%).

No specific adverse event appeared to be significantly increased in these different subgroups compared to the global population. Nevertheless, more cases of creatinine clearance <60 ml/min were observed in older patients (6.3% in patients <65 years, 36.1% in patients between 65-75 years and 65.9% in patients >75 years) and in female patients compared to male patients (19.7% *vs* 9.1%). It is to be taken into account that the number of patients >75 years was limited (n=41, 2.6% of the global population) and in the affected subgroups, patients >75 years and female patients, the mean creatinine clearance levels for these patients were already lower at inclusion in the study, compared to other subgroups. In addition, more cases of renal insufficiency and decreased CrCl <60 ml/min were reported as AEs in the CrCl subgroup <60 ml/min (7.5% and 5.4% respectively) and in the CrCl subgroup between 60-75 ml/min (none and 6.7% respectively) than in the CrCl subgroup >75 ml/min (2.7%) during FDC exposure.

Safety related to drug-drug interactions and other interactions

No new information has been provided. The wording on the interactions for the different monocomponents of the FDC are adequately implemented in the SmPC.

Discontinuation due to adverse events

As previously discussed, 38 AEs led to the withdrawal of 31 patients (9.1%) during the study period. Twenty-six of the 38 AEs, were related to study drug. The most frequent SOCs were: Investigations (2.3%), Gastrointestinal disorders (2.0%), Musculoskeletal and connective tissue disorders (1.8%) and Renal and urinary disorders (1.5%).

Post marketing experience

There is no postmarketing experience with this product since it has not been marketed yet.

2.6.1. Discussion on clinical safety

Safety profiles of fenofibrate and statin are well defined. The data analysed in the marketing authorisation application for Pravafenix were derived from literature research, published clinical trials on statin/fibrate combination use and on the conducted four clinical studies. These take into account more than 1500 patients who received the FDC: a total of 1566 patient were exposed to at least one dose of Pravafenix, 928 patients were exposed for 24 weeks and 395 patients were exposed for 1 year. Patient exposures can be considered as acceptable.

Similar safety profile was observed in both, the statin and FDC group. The most frequently reported AEs were related to muscle and musculoskeletal disorders (muscle and articular pain), gastrointestinal

disorders (abdominal pain and transit abnormalities), and investigations (increased hepatic and muscle enzyme levels).

Increase of CPK and *transaminases* was reported in all treatment groups during the efficacy and safety phases. The majority of patients experienced an increase <3 UNL. However the increase of CK was slightly more frequent during the safety phase with approximately 40% of patients who had an increase ≤3 UNL. Less than 2% of patients reported moderate increase (>3-5 UNL) of CK and less than 1% reported severe increase (>5 UNL). Similarly, less than 1% of patients reported increase of ALT >3 UNL. Thorough and regular monitoring of CK levels prior to and during the therapy is therefore advised in the SmPC of Pravafenix.

Homocysteine blood control has been performed in study FENOPRA III-06-1. This showed a statistically significant increase in levels especially in the FDC group in high and very high cardiovascular risk patients. This increase is correlated to the decrease of the clearance of creatinine and is reversible after drug withdrawal. The CHMP considered that the homocysteine increase could be of concern as the proposed indication of the fixed dose combination of pravastatin and fenofibrate is intended to be used in patients with mixed dyslipidemia and at high cardiovascular risk. This finding was observed in the FIELD study and confirmed in the ACCORD study, and could be important in patients with moderate renal failure compared to those with mild renal failure or normal renal function. However, no conclusion can be drawn up to now regarding a possible link between increased homocysteine and the cardiovascular risk. Additionally, increased homocysteine is correlated to the decrease of creatinine clearance which is also a concern related to fenofibrate use. This issue will remain under close monitoring. Pravafenix is contraindicated in patients with severe and moderate renal impairment and regular monitoring of renal function is recommended, as per the SmPC.

Eight cases of *neoplasm* (breast cancer, bronchial carcinoma, lymphoma, 2 lung neoplasm, ovarian cancer, prostate cancer, and melanoma) have been reported during the safety phase in patients receiving FDC therapy. All cases were considered unrelated to treatment. Safety review of statins and risk of cancer following the publication of the PROSPER study in 2002 was conducted. Although it showed higher incidence of new cancer diagnoses in patients on pravastatin *vs* placebo, the assessment of available data does not change the positive benefit-risk profile of a statin. The available clinical data are reassuring and provide no evidence for an increased risk of cancer in the general patient population treated with a statin for up to 5 years, although no conclusive data are available concerning effect of statins on cancer risk in the elderly (≥ 70 years). However, monitoring of neoplasm cases in clinical trials and during post-marketing use in patients treated with statins in general is recommended.

The CHMP requested a description of cases of myopathy, myositis and rhabdomyolysis and hepatitis reported in ACCORD study. It was concluded that based on these results, and the results from the studies conducted with Pravafenix, no safety concern was identified for the muscle or hepatic disorders. This, however, is to be expected especially when considering the low number of patients exposed to FDC in at least one year. No rhabdomyolysis was reported and only one patient experienced increased CPK >10 UNL associated to muscle disorders in pravastatin group. Nevertheless, acknowledging that rhabdomyolysis is an acute and potentially fatal condition of skeletal muscle, which may develop at any time during treatment and that it is known that the risk of muscle toxicity is increased when a fibrate and a HMG-CoA reductase inhibitor are administered together, myopathy must be considered in any patient presenting with unexplained muscle symptoms such as pain or tenderness, muscle weakness, or muscle cramps. In such cases CK levels should be measured. The potential benefit/risk ratio of Pravafenix should be closely assessed before treatment initiation and patients should be monitored for any signs of muscle toxicity, as stated in the SmPC for Pravafenix.

Given that only 35% of patients (532) in FDC treatment group were exposed during 52 weeks, and less than 10% were exposed to FDC during 64 weeks (148), no accurate conclusion can be drawn regarding long term safety data of FDC. No data was also available regarding the elderly, patients with renal and hepatic impairment. Pravafenix is contraindicated in patients with moderate to severe renal impairment, as mentioned earlier.

The combination of both therapies with similar identified safety concerns (i.e. muscle disorders, increased hepatic and muscle enzymes, pancreatic, interstitial fibrosis) could probably lead to a demonstration of these adverse events. Therefore, the CHMP requested conduct of two post-authorisation studies that will contribute to a better definition of Pravafenix safety profile.

From the safety database all the adverse reactions reported in clinical trials and post-marketing use of fenofibrate with statins have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

As expected, some of the AEs observed with Pravafenix are more pronounced than those for the monotherapies, however, no new or significant safety concern has been identified taking into account the clinical studies conducted with the FDC and the results of the published investigations including the ACCORD study. The most frequently reported AEs related to study drug were renal and urinary disorders, which included decreased levels of renal creatinine, increases transaminases and musculoskeletal disorders, all of them expected according to the SmPC of both actives substances in monotherapy. The safety profile of Pravafenix is adequately reflected in the SmPC of this medicinal product.

2.7. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements. In addition, the CHMP considers that it is necessary to conduct a pharmacovigilance inspection before end of 2011, in order to verify the accuracy and the successful implementation of the corrective actions following a recent pharmacovigilance inspection performed in 2010.

Risk Management Plan

The MAA submitted a risk management plan.

Table Summary of the risk management plan:

Safety issues	**Agreed pharmacovigilance activities**	**Agreed risk minimisation activities**
MUSCULOSKELETAL AND CONNECTIVE DISORDERS (Important identified risk): Myopathy, myositis, myalgia, muscle disorder, blood creatine phosphokinase abnormal, muscle enzyme increase	▪ Routine pharmacovigilance ▪ Post-authorisation safety study	• Contraindication in section 4.3 of the SPC • Special warning and precaution of use in section 4.4 of the SPC • Listed as adverse reaction in section 4.8 of the SPC
HEPATOBILIARY DISORDERS (Important identified risk): Transaminases increased, hepatic failure, hepatic pain, hepatotoxicity, hepatitis, blood bilirubin abnormal, hepatic enzyme abnormal, gamma-glutamyltransferase abnormal, transaminases abnormal	▪ Routine pharmacovigilance ▪ Post-authorisation safety study	• In Section 4.2 of the SPC (Posology and method of administration), Pravafenix is not recommended in patients with moderate hepatic insufficiency • Contraindication in section 4.3 of the SPC • Special warning and precaution of use in section 4.4 of the SPC • Listed as adverse reaction in section 4.8 of the SPC

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
RENAL AND URINARY DISORDERS (Important identified risk): Blood creatine abnormal, Blood creatinine abnormal, creatinine renal clearance abnormal, renal failure, renal disorder, blood urea abnormal, glomerular filtration rate abnormal, red blood cells urine positive, urine analysis abnormal.	▪ Routine pharmacovigilance ▪ Post-authorisation safety study	• In Section 4.2 of the SPC (Posology and method of administration), PRAVAFENIX is contraindicated in patients with moderate to severe renal impairment • Contraindication in section 4.3 of the SPC • Special warning and precaution of use in section 4.4 of the SPC • Listed as adverse reaction in section 4.8 of the SPC
CHOLELITHIASIS (Important identified risk): Cholelithiasis, Gallbladder disorder.	▪ Routine pharmacovigilance ▪ Post-authorisation safety study	• Contraindication in section 4.3 of the SPC • Special warning and precaution of use in section 4.4 of the SPC • Listed as adverse reaction in section 4.8 of the SPC
THROMBOEMBOLIC EVENTS (Important identified risk): Pulmonary embolism, Deep vein thrombosis.	▪ Routine pharmacovigilance ▪ Post-authorisation safety study	• Special warning and precaution of use in section 4.4 of the SPC • Listed as adverse reaction in section 4.8 of the SPC
PANCREATITIS (Important identified risk): Pancreatitis, pancreatitis acute, pancreatic disorder, pancreatic enzymes abnormal, blood amylase increased.	▪ Routine pharmacovigilance ▪ Post-authorisation safety study	• Contraindication in section 4.3 of the SPC • Special warning and precaution of use in section 4.4 of the SPC • Listed as adverse reaction in section 4.8 of the SPC
INCREASED RISK OF MYOPATHY (Important potential risk): Rhabdomyolysis	▪ Routine pharmacovigilance ▪ Post-authorisation safety study	• Contraindication in section 4.3 of the SPC • Special warning and precaution of use in section 4.4 of the SPC • Listed as adverse reaction in section 4.8 of the SPC
INCREASED RISK OF HEPATIC EVENTS (Important potential risk): Hepatic failure.	▪ Routine pharmacovigilance ▪ Post-authorisation safety study	• In Section 4.2 of the SPC (Posology and method of administration), PRAVAFENIX is not recommended in patients with moderate hepatic insufficiency • Contraindication in section 4.3 of the SPC • Special warning and precaution of use in section 4.4 of the SPC • Listed as adverse reaction in section 4.8 of the SPC

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
INCREASE RISK OF PANCREATIC EVENTS (Important potential risk): Pancreatitis.	▪ Routine pharmacovigilance ▪ Post-authorisation safety study	• Contraindication in section 4.3 of the SPC • Special warning and precaution of use in section 4.4 of the SPC • Mentioned as adverse reaction in section 4.8 of the SPC
BLOOD HOMOCYSTEINE INCREASED (Important potential risk): Blood homocysteine increased, blood homocysteine abnormal, hyperhomocysteinaemia.	▪ Routine pharmacovigilance	No risk minimisation activity is considered necessary for the time being
DIABETES MELLITUS AGGRAVATED (Important potential risk): Diabetes mellitus aggravated, diabetes mellitus exacerbated, worsening of diabetes, hyperglycaemia, blood glucose abnormal	• Routine pharmacovigilance	• Listed as adverse reaction in section 4.8 of the SPC
INTERSTITIAL PNEUMOPATHY (Important potential risk): Interstitial lung disease, pulmonary fibrosis.	• Routine pharmacovigilance	• Special warning and precaution of use in section 4.4 of the SPC • Mentioned as adverse reaction in section 4.8 of the SPC
PHOTOTOXICITY (Important potential risk): Photosensivity reaction, photosensitivity allergic reaction, retinal phototoxicity.	• Routine pharmacovigilance	• Contraindication in section 4.3 of the SPC • Listed as adverse reaction in section 4.8 of the SPC
OFF LABEL USE (Important potential risk)	• Routine pharmacovigilance • Drug Utilisation Study	No risk minimisation activity is considered necessary for the time being
INAPPROPRIATE MONITORING DURING TREATMENT (Important potential risk)	• Routine pharmacovigilance • Drug Utilisation Study	No risk minimisation activity is considered necessary for the time being
PATIENTS ABOVE THE AGE OF 75 YEARS (Important missing information)	• Routine pharmacovigilance	• In Section 4.2 of the SPC (Posology and method of administration), it is stated that "….Limited safety data on Pravafenix is available in patients >75 years of age and care should be exercised."
LONG-TERM SAFETY PROFILE OF THE PRODUCT (Important missing information)	• Routine pharmacovigilance	No risk minimisation activity is considered necessary for the time being
EXCLUSION'S CRITERIA (Important missing information) Patients not studied during clinical trials: - Uncontrolled hypertension (SBP > 160 mmHg or DBP > 95 mmHg) under blood pressure treatment.	• Routine pharmacovigilance	No risk minimisation activity is considered necessary for the time being

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
- Diabetes requiring insulin. - Uncontrolled diabetes with HbA1c > 8.5%. - Patients who had an acute cardiovascular episode within the 6 months previous to the start of the trial (3 months or with a history of coronary angioplasty with mounting of a stent within the past 6 months).		
OTHER ETHNICAL SUBGROUP POPULATION THAN CAUCASIAN (Important missing information)	• Routine pharmacovigilance	No risk minimisation activity is considered necessary for the time being
NEOPLASM (Important missing information)	• Routine pharmacovigilance	No risk minimisation activity is considered necessary for the time being

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

However, the CHMP requested for an additional pharmacoviginalnce post-authorisation safety study to be carried out after placing the product on the market.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8. Benefit-Risk Balance

Benefits

Statins are the first line treatment in the management of dyslipidaemia. Pravastatin is a statin of middle potency that has shown to be effective in cardiovascular prevention in a wide range population. The main mechanism of action of statins in CV prevention is their effect on lipid levels, mainly on LDL-cholesterol.

The effect of lipid lowering agents, especially of statins, on LDL-cholesterol is accepted as a validated surrogate for the evaluation of CV prevention. Whether this surrogacy value can be extrapolated to drugs other than statins could be further discussed.

Fibrates have been shown to have a modest effect on LDL, but quite a marked effect on TG and HDL-cholesterol. Outcome studies conducted with the different fibrates have shown inconsistent results in terms of outcome, and, in some cases, possibly worrying results in overall mortality.

This issue was extensively discussed during Article 31 Referral on fibrates and the CHMP provided its final opinion which results in a newly accepted indication for fibrates: "Mixed hyperlipidaemia in patients at high CV risk in addition to a statin when TG and HDL cholesterol are not adequately controlled".

Beneficial effects

Effects on lipid parameters. As expected, results observed in the initial Pravafenix clinical dossier have shown a more potent effect of fenofibrate on TG and HDL-C, while pravastatin is superior in reducing total cholesterol and LDL-C.

Indeed, the co-administration of statin and fibrates has a role in patient treatment with insufficient response to statins, and in this particular case, to pravastatin. This is recognised in clinical guidelines and omitting this option would leave a substantial portion of patients at high CV risk, particular those with elevated TG and/or low HDL despite full-dosed statin therapy, with a very limited treatment options.

In the overall clinical programme, the combination showed mainly a decrease in TG levels with an incremental increase in HDL-C levels and in some cases further reduction in total cholesterol and LDL-C levels. There results are in line with results obtained in the ACCORD study in a selected population of type 2 diabetic patients.

Effects on lipid parameters in a specific subgroup of dyslipidaemic patients. Only benefit on lipid parameters was effectively demonstrated in the subgroup of patients with mixed dyslipidaemia defined as TG >204mg/dl AND HDL-C <34mg/dL levels.

Uncertainty in the knowledge about the beneficial effects

Uncertainties of cardiovascular events in overall dyslipidaemic patients including women: This issue was extensively discussed during Article 31 Referral on fibrates and the CHMP provided its final opinion which results in a newly accepted indication for fenofibrate: Mixed hyperlipidaemia in patients at high CV risk in addition to a statin when TG and HDL cholesterol are not adequately.

Uncertainties on the equipotency of statins: The CHMP does not support the statin equipotency as originally claimed by the applicant. The potency of pravastatin as compared to other statins is lower and the individual response of a patient cannot be generalised to the whole population. In clinical practice, there is no reason for switching patients controlled by one statin to Pravafenix. Therefore, the indication is to be limited to pravastatin 40mg and to patients that are sufficiently controlled for their LDL-C levels. Indeed, this is of particular importance because treatment with pravastatin is not as potent as other statins in reducing LDL-C.

Risks

Unfavourable effects

The long term safety data regarding the comparison of simvastatine alone to simvastatine/fenofibrate was provided in the ACOORD study. No safety signal regarding cholelithiasis, pancreatic, thromboembolic events was identified during this study. However, no firm conclusion can be drawn regarding the long term use of the fixed dose combination of fenofibrate/statin regarding the increased risk of renal failure, muscle disorders, hepatitis, cholelithiasis and pancreatitis. Furthermore, it should be noted that in 16% of patients in the ACCORD study, the dose of fenofibrate has been reduced due to a decrease of renal glomerular filtration. The increased level of homocysteine as described in the FIELD study has also been confirmed in the ACCORD study.

Uncertainty in the knowledge about the unfavourable effects

No new safety profile can be identified based on the use of the fixed dose combination of fenofibrate/statin as the ACCORD study was insufficiently powered.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The recently published ACCORD study does not appear to support the extensive use of a fenofibrate/simvastatin combination therapy to reduce cardiovascular events in the majority of dyslipidaemic high CV risk patients with type 2 diabetic patients. Indeed, only beneficial effects on cardiovascular endpoints were observed in patients with high TG and low HDL-C values. This has also been extensively discussed during Article 31 referral on fenofibrate. Thus, finally, only an indication that will be limited to this specific population subgroup can be granted by the CHMP.

Benefit-risk balance

Based on the provided data, benefits on lipid parameters (surrogate endpoints) were effectively demonstrated in the subgroup of patients with mixed dyslipidaemia defined by TG >204mg/dl and HDL-C <34mg/dL levels. Results are however insufficient to recommend an extensive use in patients with high TG or low HDH-C levels as originally claimed. Nevertheless, the importance whether these biological effects could translate into benefits on cardiovascular endpoints was considered by the CHMP during the first step of the Pravafenix procedure in the context of the long term use of the statin/fenofibrate combination. After reviewing data from the ACCORD study, it would appear that there is a detrimental effect of the long term use of a statin/fenofibrate combination on women. This gender issue has been extensively discussed during referral on fibrates. Overall, the biological benefit expressed in the newly worded and approved indication can be recognised for the pravastatin/fenofibrate combination.

2.8.1. Discussion on the benefit-risk balance

Based on the provided data and the rationale above, Pravafenix is aimed to offer an alternative to a specifically targeted population; i.e. high CHD-risk adult patients with mixed dyslipidaemia characterised by high TG and low HDL-C whose LDL-C are adequately controlled while on a treatment with pravastatin 40mg monotherapy.

Overall, the biological effect expressed in the newly worded and approved indication can be recognised for the pravastatin/fenofibrate combination.

Risk management plan

Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- Pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

- No additional risk minimisation activities were required beyond those included in the product information.

2.9. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Pravafenix in *the treatment of high coronary heart disease (CHD) -risk adult patients with mixed dyslipidaemia characterised by high triglycerides and low HDL-cholesterol levels whose LDL-C levels are adequately controlled while on a treatment with pravastatin 40 mg monotherapy* was favourable and therefore recommended the granting of the marketing authorisation.