HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

Opinion

22 January 2014

LIPANTHYL 67 mg micronised, capsule
B/60 (CIP 335 271-6)
B/90 (CIP 335 272-2)

LIPANTHYL 145 mg, film-coated tablet
B/30 (CIP 369 641-0)
B/90 (CIP 369 642-7)

LIPANTHYL 160 mg, film-coated tablet
B/30 (CIP 355 373-9)
B/90 (CIP 371 780-4)

LIPANTHYL 200 mg micronised, capsule
B/30 (CIP 332 635-7)
B/90 (CIP 371 785-6)

FENOFIBRATE FOURNIER 100 mg, capsule
B/30 (CIP 362 756-7)

FENOFIBRATE FOURNIER 300 mg, capsule
B/30 (CIP 361 735-6)

SECALIP 100 mg, capsule
B/48 (CIP 323 764-2)

SECALIP 300 mg, capsule
B/30 (CIP 330 030-0)

Applicant: ABBOTT PRODUCTS SAS

INN	fenofibrate
ATC Code (2010):	C10AB05 (Lipid modifying agents, plain - fibrates)
Reason for the review	**Renewal of inclusion** **Extension of indication**
List concerned	**National Health Insurance** (French Social Security Code L.162-17)

Indications concerned	**<u>Renewal of inclusion</u>:** **"LIPANTHYL, FENOFIBRATE FOURNIER, SECALIP are indicated as an adjunct to an appropriate diet and other non-pharmacological treatments (e.g. exercise, weight reduction) for the following:** **- treatment of severe hypertriglyceridaemia with or without low HDL cholesterol,** **- mixed hyperlipidaemia when a statin is contraindicated or not tolerated,** **"In children (LIPANTHYL 67 mg, FENOFIBRATE FOURNIER and SECALIP 100 mg only): see sections 4.2 and 4.4 of the SPC"** **<u>Extension of indication:</u>** **"LIPANTHYL, FENOFIBRATE FOURNIER, SECALIP are indicated as an adjunct to an appropriate diet and other non-pharmacological treatments (e.g. exercise, weight reduction) for the following:** **mixed hyperlipidaemia in patients at high cardiovascular risk, in addition to a statin when triglycerides and HDL cholesterol levels are not adequately controlled."**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date (national): LIPANTHYL 67 mg: 25/11/1991 LIPANTHYL 145 mg: 19/09/2005 LIPANTHYL 160 mg: 09/10/2000 LIPANTHYL 200 mg: 20/03/1990 FENOFIBRATE FOURNIER 100 mg: 17/06/1987 FENOFIBRATE FOURNIER 300 mg: 28/03/2003 SECALIP 100 mg: 17/06/1987 SECALIP 300 mg: 20/11/1987 Date of extension of indication (patients at high cardiovascular risk): 27/02/2012 for the proprietary medicinal products registered via the national procedure 22/02/2012 for the proprietary medicinal products registered via the mutual recognition procedure
Prescribing and dispensing conditions/special status	List II
ATC Classification	2011 C Cardiovascular system C10 Lipid modifying agents C10A Lipid modifying agents, plain C10AB Fibrates C10AB05 fenofibrate

02 BACKGROUND

Examination of the proprietary medicinal products renewed on the list of medicines refundable by National Health Insurance for a 5 year period starting on 22 July 2007 (Official Gazette of 20 November 2008).
Since the previous renewal of inclusion in 2007, following a standardisation of the SPC for fibrates by the EMA, a new indication in patients at high cardiovascular risk who have mixed dyslipidaemia was validated by the Marketing Authorisation in an amendment dated 27 February 2012; this indication will also be reviewed in this opinion.

03 CHARACTERISTICS OF THE MEDICINAL PRODUCT

03.1 Therapeutic indications[1]

"LIPANTHYL, FENOFIBRATE FOURNIER, SECALIP are indicated as an adjunct to an appropriate diet and other non-pharmacological treatments (e.g. exercise, weight reduction) for the following:

- treatment of severe hypertriglyceridaemia with or without low HDL cholesterol,
- mixed hyperlipidaemia when a statin is contraindicated or not tolerated,
- **mixed hyperlipidaemia in patients at high cardiovascular risk, in addition to a statin when triglycerides and HDL cholesterol are not adequately controlled.**"

"In children (LIPANTHYL 67 mg, FENOFIBRATE FOURNIER and SECALIP 100 mg only): see sections 4.2 and 4.4 of the SPC"

[1] The wording of the indications underwent European standardisation and has been validated by an amendment to the Marketing Authorisation dated 27/02/2012.

03.2 Dosage (LIPANTHYL 160 mg)

"In adults: the recommended dose is one tablet containing 160 mg of fenofibrate a day. The patients receiving one capsule of LIPANTHYL 200 mg micronised can switch to one LIPANTHYL 160 mg film-coated tablet without adjusting the dose.

Elderly subjects: the usual adult dose is recommended.

Renal impairment: a reduction in the dosage is recommended for those with renal impairment. Use of other forms containing a lower dose of active substance (67 mg micronised fenofibrate capsule or 100 mg standard fenofibrate capsule) is recommended for these patients.

In children: use of the 160 mg form is contraindicated.

Hepatic impairment: this disease did not undergo a clinical study.

Dietary measures initiated before the treatment should be continued.

If after several months (e.g. 3 months) of administrating fenofibrate the serum lipid levels have not dropped sufficiently, other treatments or complementary therapies should be considered".

For the other proprietary medicinal products and the other dosages, please refer to their SPC.

03.3 Contraindications (LIPANTHYL 160 mg)

- "Hepatic insufficiency (including biliary cirrhosis and unexplained persistent liver function abnormalities, for example persistent increase in serum transaminases).
- Renal impairment.
- In children (under 18 years of age).
- Hypersensitivity to the active substance or to any of the excipients.
- Known photoallergy or phototoxic reaction during treatment with fibrates or ketoprofen.
- Gallbladder disease.
- Chronic or acute pancreatitis with the exception of acute pancreatitis due to severe hypertriglyceridaemia.

LIPANTHYL 160 mg film-coated tablet should not be prescribed to patients who are allergic to cashew, groundnut oil, soy lecithin or one of its derivatives due to the risk of hypersensitivity."

For the other proprietary medicinal products and the other dosages, please refer to their SPC.

03.4 Special warnings and precautions for use (LIPANTHYL 160mg)

"Before starting any fenofibrate treatment, the secondary causes of hypercholesterolaemia, such as uncontrolled type 2 diabetes, hypothyroidism, nephrotic syndrome, dysproteinaemia, hepatic cholestasis, pharmacological treatment, alcoholism, should be treated adequately.
For the hyperlipiaemic patients taking oestrogen or contraceptives containing oestrogen, it is necessary to ascertain whether the hyperlipidaemia is of a primary or secondary nature (possible increase in lipid levels caused by the oral administration of oestrogen) etc.
Muscle: Muscle toxicity, including very rare cases of rhabdomyolysis, has been reported with administration of fibrates and other lipid lowering agents. The incidence of these disorders increases in cases of hypoalbuminaemia and previous renal insufficiency. Muscle toxicity should be suspected in patients presenting diffuse myalgia, myositis, muscular cramps and weakness and/or marked increases in CPK (> 5 times the upper limit of normal). In such cases, treatment

with fenofibrate should be stopped. The risk of muscle toxicity may be increased if the drug is administered with another fibrate or an HMG-CoA reductase inhibitor, particularly in cases of pre-existing muscular disease. Consequently, the co-prescription of fenofibrate with a statin should be reserved to patients with severe combined dyslipidaemia and high cardiovascular risk without any history of muscular disease. This combination therapy should be used with caution and patients should be monitored closely for signs of muscle toxicity…"

For the other proprietary medicinal products and the other dosages, please refer to their SPC.

04 SUMMARY OF PREVIOUS ASSESSMENTS

Date of opinion (reason for review)	26/09/2007 Renewal of inclusion
Indication	Isolated or combined hypercholesterolaemia and hypertriglyceridaemia (dyslipidaemia types II a, II b, IV as well as dyslipidaemia types III and V) in patients who do not respond to a suitable diet and other non-pharmacological treatments (e.g. reduction in body weight or increase in physical activity), particularly when there are associated risk factors. The treatment of secondary hyperlipoproteinaemia is indicated when hyperlipoproteinaemia persists, even when effective treatment is given for an underlying disease (e.g. dyslipidaemia in diabetics). Following a regime is always a must.
AB	Substantial

05 ANALYSIS OF NEW AVAILABLE DATA

05.1 Efficacy

5.1.1. Severe hypertriglyceridaemia

The company reports two references:

- an analysis of the FIELD[2] study data in a patient sub-group, defined after the event, which will not be discussed in this opinion in view of its methodology;
- a prospective follow-up of a cohort of patients (PRIME),[3] the objective of which was to compare the occurrence of death from any cause in 10 years depending on the lipid status of the patients and whether or not they have been exposed to lipid lowering treatments (statins, fibrates). Given the methodological biases (no routine of experiments, non comparable groups at baseline, development of risk factors and treatments over time not taken into consideration in the analysis….), this follow-up study will not be discussed in this opinion.

5.1.2. Mixed hyperlipidaemia when a statin is contraindicated or not tolerated

The company has not filed any clinical data in this indication.

[2] Scott et al. Effects of fenofibrate treatment on cardiovascular disease risk in 9 795 individuals with type 2 diabetes and various components of metabolic syndrome : the fenofibrate Intervention and event lowering in diabetes (FIELD) study. Diabetes Care.2009; 32: 493-8.

[3] Gardette et al. Ten-year all-cause mortality in presumably healthy subjects on lipid-lowering drugs (from epidemiological study of myocardial infarction [PRIME] prospective cohort. Am J Cardiol 2009; 103: 381-6.

5.1.3. Mixed hyperlipidaemia in patients at high risk of cardiovascular disease

Following a standardisation of SPCs relating to fibrates by the EMA, an extension of indication has been approved by the Marketing Authorisation in amendments dated 22 and 27 February 2012 with the following wording:
"Mixed hyperlipidaemia in patients at high cardiovascular risk, in addition to a statin when triglycerides and HDL cholesterol are not adequately controlled."

For this indication, the company reports six references:

- one study whose objective was to evaluate the benefit of the combination of fenofibrate with a statin in terms of morbidity and mortality: the ACCORD[4],[5] study, which compared the benefit of adding fenofibrate to simvastatin versus simvastatin monotherapy in terms of the occurrence of cardiovascular events in 5518 patients with type 2 diabetes; the results of this study were included in the SPC for LIPANTHYL.
- five studies whose objective was to evaluate the benefit of the combination of fenofibrate with a statin on the lipid parameters:
    - The Athyros 2002[6] study, which compared the benefit of adding fenofibrate 200 mg treatment to atorvastatin 20 mg versus atorvastatin 20 mg monotherapy in terms of lipid parameters in 120 patients with type 2 diabetes,
    - The Farnier 2010[7] study and its open label follow-up phase in 2011,[8] which compared fixed-dose combination fenofibrate/pravastatin 160/40 mg versus pravastatin 40 mg monotherapy on the lipid parameters in 211 patients at high cardiovascular risk uncontrolled with pravastatin 40 mg monotherapy,
    - The Farnier 2011[9] study, which compared fixed-dose combination fenofibrate/pravastatin 160 mg/40 mg versus simvastatin 20 mg monotherapy on the lipid parameters in 291 patients with type 2 diabetes uncontrolled with simvastatin 20 mg monotherapy,
    - The Derosa 2002[10] study, which compared the benefit of adding fenofibrate 200 mg treatment to atorvastatin 20 mg versus atorvastatin 20 mg monotherapy in terms of lipid parameters in 120 patients with type 2 diabetes.

The Athyros 2002 and Derosa 2002 studies, performed in patients not previously treated with lipid-lowering agents, will not be discussed in this opinion because the included population does not comply with the Marketing Authorisation, which specifies "mixed hyperlipidaemia in patients at high cardiovascular risk, **in addition to a statin when triglycerides and HDL cholesterol are not adequately controlled.**"
Likewise, the studies presented only in the form of abstracts will not be detailed.

Morbidity and mortality study: ACCORD

This randomised study comparing fenofibrate + simvastatin versus simvastatin monotherapy (simvastatin administered in open-label combined with fenofibrate or a placebo) evaluated the efficacy of these treatments in 5518 patients with type 2 diabetes monitored, on average, over 4.7 years.
The primary efficacy endpoint was a combined endpoint which included non-fatal myocardial infarctions, non-fatal strokes and deaths due to cardiovascular disease.

[4] The ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. NEJM 2010; 362: 1563-74.
[5] The ACCORD lipid study; implications for treatment of dyslipidemia in type 2 diabetes mellitus. Clin.Lipidol 2011: 9-20
[6] Athyros et al. Atorvastatine and micronized fenofibrate alone and combination in type 2 diabetes with combined hypelipidemia. Diabetes care 2002; 25: 1198-1202.
[7] Farnier M. et al. Efficacy and safety of adding fenofibrate 160 mg in high-risk patients with mixed hyperlipidemia not controlled by pravstatin 40 mg monotherapy. Am J Cardiol 2010; 106: 787-92.
[8] Farnier M. et al. Long-term safety and efficacy of fenofibrate/pravastatin combination therapy in high risk patients with mixed hyperlipidemia not controlled by pravastatin therapy. Current Medical Research & opinion 2011; 27: 2165-73.
[9] Farnier M. et al. Fixed dose combination fenofibrate/pravastatin 160/40 mg versus simvastatin 20 mg monotherapy in adults with type 2 diabetes and mixed hypercholesterolemia uncontrolled with statin 20 mg : a double-blind, randomized comparative study. Clinical tharapeutics 2011; 33.
[10] Derosa G. et al. Fenofibrate, simvastatin and their combination in the management of dyslipidemia in type 2 diabetic patients. Current medical research and opinions; 25: 1973-83.

After an average follow-up of 4.7 years, no significant difference was observed for the combined primary endpoint which included non-fatal myocardial infarctions, non-fatal strokes and death due to heart disease between the fenofibrate plus simvastatin combination and simvastatin monotherapy. 291 events in the fenofibrate + simvastatin group versus 310 in the simvastatin monotherapy group, RR 0.92 [0.79-1.08], NS.

A significant reduction was observed only in the sub-group of dyslipidaemic patients (defined as those in the lowest tertile for HDL-C [≤ 34 mg/dl or 0.88 mmol/l] and the highest tertile for TG [≥ 204 mg/dl or 2.3 mmol/l]) defined beforehand: RR 0.69 [0.49-0.97], p = 0.03; reduction in absolute risk: 4.95%. This sub-group corresponded to 17% of the total study population.

On the basis of the results of this study, the CHMP[11], on 28/02/2011, recommended the extension of indication for fenofibrate in addition to statins in patients at high cardiovascular risk when triglycerides and HDL cholesterol are not adequately controlled.

Study on the lipid parameters

Studies	Type of study	Numbers N	Inclusion criteria	Results: Primary endpoint
Farnier **2010**[7] **2011**[8]	Comparative study Fixed-dose combination of pravastatin 40 mg + fenofibrate 160 mg **vs** pravastatin 40 mg Randomised and double-blind Duration: 12 weeks 52-week open-label follow-up (all the patients who completed the 12 weeks of study were included in the follow-up and treated with the combination)	N=248 Pravastatin + fenofibrate: 123 Pravastatin: 125 N=211	Adults at high cardiovascular risk[12] Mixed dyslipidaemia **uncontrolled** with pravastatin 40 mg LDL ≥ 1 g/l 1.5 ≤ TG > 4 g/l	<u>Change in non-HDL cholesterol compared with the initial state</u>: pravastatin + fenofibrate versus pravastatin after 12 weeks: **-14.1% versus -6.1%, difference -8%, p<0.002** <u>52-week open-label follow-up</u>: Significant reduction in non-HDL cholesterol compared with what it was at baseline, p<0.0001
Farnier **2011**[9]	Comparative study Fixed-dose combination of pravastatin 40 mg + fenofibrate 160 mg **vs** simvastatin 20 mg Randomised and double-blind Duration: 12 weeks 12-week open-label follow-up (all the patients who completed the 12 weeks of study were included in the follow-up and treated with the combination)	N=289 Pravastatin + fenofibrate: 144 Simvastatin: 145 N=281	Adults with type 2 diabetes Mixed dyslipidaemia **uncontrolled** with simvastatin 20 mg Non-HDL > 1.3 g/l or LDL ≥ 1 g/l and 1.5 ≤ TG > 6 g/l	<u>Change in non-HDL cholesterol compared with the initial state</u>: pravastatin + fenofibrate versus simvastatin after 12 weeks: **-12.9 (1.8)% versus -6.8 (1.8)%, difference -6.1%, p=0.008** <u>12-week open-label follow-up</u>: Significant reduction in non-HDL cholesterol compared with what it was at baseline, p<0.0001

[11] Assessment report for fenofibrate, bezafibrate, ciprofibrate and gemfibrozil containing products. EMA, 28 February 2011.

[12] Defined by at least one of the following criteria: a history of coronary heart disease, a history of atherosclerosis, risk of coronary heart disease > 20% according to Framingham, diabetes.

05.2 Adverse effects

5.2.1. Data from clinical studies

In the ACCORD study, no significant difference was observed between the fenofibrate + simvastatin combination versus the placebo + simvastatin combination in terms of:
- muscle pain: 40.1% versus 40.5%,
- myositis/rhabdomyolysis: 0.1% in each group,
- increase in CPK 10 times the upper limit of normal: 10 patients in the fenofibrate group (0.4%) and 9 patients in the simvastatin group (0.3%).

In the Farnier study,[9] adverse effects were observed in 25/145 patients in the fenofibrate + pravastatin group (17.2%) versus 22/146 patients in the simvastatin group (15.1%). Two patients in each group discontinued their treatment on account of adverse events.
The most commonly observed adverse events (>1%) were:
- headaches: three patients versus two patients,
- gastrointestinal disorders: two versus six,
- musculoskeletal disorders: two versus one,
- skin disorders: zero versus four.

In the 12-week open-label follow-up phase, 27/281 (9.6%) of patients presented with adverse events, six of which were linked to the treatment. One serious adverse event was reported (heart failure).

5.2.2. PSUR data

The analysis of the last periodic safety update report (PSUR) covering the period from 1 August 2011 to 31 January 2013 allowed the exposure of patients to the treatment to be estimated at 5,500,000 patient-years. During this period, 1567 adverse effects were reported including 244 considered serious. The most common (N>20) were: abnormal liver enzymes, increase in CPK, skin rash, pruritus.

The Core Company Safety Information was changed in March 2013 following the validation of a signal (severe skin reactions, such as Hebra's disease, toxic epidermal necrolysis or Stevens-Johnson syndrome). This update has already been part of a variation filing procedure on 17 April 2013 for the fenofibrate-based proprietary medicinal products registered in accordance with a mutual recognition registration procedure, i.e. the dosages 145 mg and 160 mg. Submission of these same variations for other dosages registered in accordance with a national procedure was planned for the end of August 2013.

The analysis of previous periodic safety update reports (PSUR) covering the period from 4 November 2006 to 31 August 2011 allowed the exposure of patients to the treatment to be estimated at 21,440,000 patient-years. During this period, 2895 adverse effects were reported. The most common ones were as follows:
- musculoskeletal disorders (myalgia, arthralgia, muscle fatigue and rhabdomyolysis): 341,
- general health disorders (faintness, fatigue, asthenia, reduction in efficacy): 333,
- diseases of the skin and subcutaneous tissue (skin rash, pruritic rash): 221,
- gastrointestinal disorders (abdominal pain, pancreatitis, dyspepsia): 220.

5.2.3. Risk Management Plan

In June 2013, the company Abbott submitted to the health authorities in the European Union a Risk Management Plan for all fenofibrate-based proprietary medicinal products, either as a monotherapy, or in combination with simvastatin or marketed fenofibric acid.

a) **Factor leading to the RMP being written:** because of the potential risk of a cardiovascular event detected during the ACCORD study in women treated by lipid-lowering combinations. As

regards the Abbot products, the analysis was extended to include other risks (hypercholesterolaemia, cholelithiasis, pancreatitis, myopathy/rhabdomyolysis, drug-induced hepatitis, increase in CPK, photosensitivity, venous thromboembolic disease, risk of developing diabetes and hyperglycaemia with statins in addition to the *potential* risk of major cardiovascular events in women treated with a lipid-lowering combination, and increase in homocysteinaemia) which are all *identified with the exception of two of them which are potential risks: hypercholesterolaemia and misuse when taking the fenofibrate/simvastatin combination (prescription without Market Authorisation)*.

b) **Nature of data**: the large majority of data presented in the document relates to fenofibrate on account of the many years of experience with marketing, development and post-Marketing Authorisation studies.

c) **Pharmacovigilance Plan:** is a routine surveillance procedure for all the risks (identified) of AEs mentioned in the SPC for the products affected.
However, for two potential risks, a proposal to conduct a study adapted to the type of risk has been put forward:

- *potential risk of a cardiovascular event detected during the ACCORD study in women treated with lipid-lowering combinations* - double-blind versus placebo study in the USA. Submission of final version of the protocol (end of December 2013 – collaboration between AbbVie, US Department of Veterans Affairs who will be performing the study and the FDA). Planned end of study (end of January 2020). Study report one year later.
- *potential risk of misuse of the fenofibrate/simvastatin combination (prescription without Marketing Authroisation)*

– epidemiological study on use during the first two years of marketing in each country (protocol being discussed with the Pharmacovigilance Risk Assessment Committee).

5.2.4. SPC data

According to the SPC, the adverse effects most commonly reported during fenofibrate treatment are digestive, gastric and intestinal disorders (abdominal pain, nausea, vomiting, diarrhoea and flatulence) and hepato-biliary disorders (increase in transaminases).

05.3 Usage/prescription data

According to the IMS Health Permanent Survey of Medical Prescription data (moving annual total November 2012), LIPANTHYL was prescribed 1,531,000 times (91,000 prescriptions of LIPANTHYL 67 mg, 1,091,000 prescriptions of LIPANTHYL 145 mg, 209,000 prescriptions of LIPANTHYL 160 mg and 179,000 prescriptions of LIPANTHYL 200 mg).
The proprietary medicinal products LIPANTHYL 145, 160 and 200 mg are mostly prescribed in the treatment of lipid abnormalities (65.8 to 80.8% of prescriptions depending on dosages and symptoms) with an average dosage of one tablet a day.
The small number of prescriptions for LIPANTHYL 67 mg is insufficient to allow a qualitative analysis of the data.

FENOFIBRATE FOURNIER was prescribed 6000 times; the small number of prescriptions is insufficient to allow a qualitative analysis of the data.

SECALIP was prescribed 77,000 times; the small number of prescriptions is insufficient to allow a qualitative analysis of the data.

05.4 Therapeutic use

The scientific data acquired on these dyslipidaemias[13,14,15] and their treatment methods have been taken into consideration. In particular, they confirm that lipid-lowering agents, in contrast to statins (ezetimibe, fibrates, nicotinic acid, cholestyramine etc.) can be used if there is a specific lipid abnormality (hypertriglyceridaemia, hypo-HDLaemia etc) particularly in the event of intolerance or contraindication to statins.

Fenofibrate can also be used in combination with a statin in patients at high cardiovascular risk presenting with mixed hyperlipidaemia when triglycerides and HDL cholesterol are not adequately controlled.
In the other situations, the statin-fibrate combination should be avoided given the risk of muscle disorder which may be increased and in particular in the event of a pre-existing muscle disease.

06 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee believes that the conclusions of its previous opinion of 26 September 2007 do not need to be changed.

06.1 Actual benefit

◗ The cardiovascular diseases promoted by dyslipidaemia may be life-threatening due to complications.

◗ For the majority of patients with dyslipidaemia, the treatment needs are covered by the use of statins (atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin), which demonstrated a benefit in terms of morbidity and mortality events.

◗ The fenofibrate-based proprietary medicinal products (LIPANTHYL, SECALIP, FENOFIBRATE FOURNIER) are intended as preventive treatment.

◗ The efficacy/adverse effects ratio is modest.
The efficacy of combining fenofibrate with a statin in terms of morbidity and mortality has only been demonstrated in diabetic patients in a sub-group of patients with HDL-C levels of ≤ 0.34 g/l and TG levels of ≥ 2.04 g/l (ACCORD study).

◗ In the case of hypertriglyceridaemia, these proprietary medicinal products are first-line therapies only in patients with severe hypertriglyceridaemia where hygiene and diet measures are ineffective, particularly in their aim of preventing risks of pancreatitis.
In the case of mixed hyperlipidaemia, these proprietary medicinal products should be prescribed as a second-line therapy only in patients for whom statins are contraindicated or poorly tolerated.
In patients at high cardiovascular risk, in addition to a statin when triglycerides and HDL cholesterol are not adequately controlled, these proprietary medicinal products are second-line therapies. The Committee issues a reminder that the efficacy in terms of morbidity and mortality has only been demonstrated in diabetic patients (ACCORD study).

There are treatment alternatives.

[13] Prise en charge thérapeutique du patient dyslipidémique Afssaps [French Healthcare Product Safety Agency] recommendations, March 2005.
[14] Guidelines for the management of dyslipidaemias. ESC/EAS 2011, European Heart Journal; 32: 1769-818.
[15] "Efficacité et efficience des hypolipémiants: Une analyse centrée sur les statines »

Given all these points, the Committee estimates that the actual benefit of LIPANTHYL, SECALIP and FENOFIBRATE FOURNIER, together with a suitable diet and other non-pharmacological treatments (e.g. exercise, weight reduction) remains substantial for the following:

- **severe hypertriglyceridaemia with or without low levels of HDL cholesterol,**
- **mixed hyperlipidaemia when a statin is contraindicated or not tolerated.**

Taking account of all these points, the Committee considers that the actual benefit of LIPANTHYL, SECALIP and FENOFIBRATE FOURNIER is substantial in the extension of indication "together with a suitable diet and other non-pharmacological treatments (e.g. exercise, weight reduction) in the case of mixed hyperlipidaemia in patients at high cardiovascular risk, in addition to a statin when triglycerides and HDL cholesterol are not adequately controlled."

07 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance in the following indications:

" - **treatment of severe hypertriglyceridaemia with or without low HDL cholesterol,**
- **mixed hyperlipidaemia when a statin is contraindicated or not tolerated,**
- **in children (LIPANTHYL 67 mg, FENOFIBRATE FOURNIER and SECALIP 100 mg monotherapy)"**

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance in the indication "mixed hyperlipidaemia in patients at high cardiovascular risk, in addition to a statin when triglycerides and HDL cholesterol are not adequately controlled".

◗ Proposed reimbursement rate: 65%

◗ Packaging:

B/30: suitable for a 1-month treatment. B/90: suitable for a 3-month treatment.

◗ Special requests:

The Committee recommends that the initial prescription in the extension of indication "together with a suitable diet and other non pharmacological treatments (e.g. exercise, weight reduction) in the case of mixed hyperlipidaemia in patients at high cardiovascular risk, in addition to a statin when triglycerides and HDL cholesterol are not adequately controlled" is restricted to specialists (cardiologists, endocrinologists and lipidologists).