



HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

27 May 2009

Review of the dossier of the proprietary drugs included on the list of reimbursable medicines for a period of 5 years by the order of 20.12.2008 (JO of 28.12.2008)

EZETROL 10 mg, tablets in unit dose peelable blisters
B/28 (CIP code: 362 269-9)

EZETROL 10 mg, tablets in blister strips
B/28 (CIP code: 362 270-7)

Applicant: MERCK SHARP & DOHME-CHIBRET

Ezetimibe
ATC code: AC10AX09

List I

Date of Marketing Authorisation: 11 June 2003

Reason for request: Renewal of inclusion and re-assessment of the IAB in accordance with article R-163 of the Social Security Code and following the Ministry of Health request.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Ezetimibe

1.2. Indications

“Primary hypercholesterolemia

EZETROL co-administered with an HMG-CoA reductase inhibitor (statin) is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia who are not appropriately controlled with a statin alone. EZETROL monotherapy is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated.

Homozygous familial hypercholesterolaemia (HoFH)

EZETROL co-administered with a statin is indicated as adjunctive therapy to diet for use in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).

Homozygous sitosterolaemia (phytosterolaemia)

EZETROL is indicated as adjunctive therapy to diet for use in patients with homozygous familial sitosterolaemia.

Studies demonstrating the efficacy of EZETROL in prevention of the complications of atherosclerosis have not yet been completed.”

1.3. Dosage (see SPC)

“Route of administration is oral. The patient should be on an appropriate lipid-lowering diet throughout the period of treatment with EZETROL.

The recommended dose is one EZETROL 10 mg tablet daily. EZETROL can be administered at any time of the day, with or without food.

When EZETROL is added to a statin, the usual initial dose or the already established dose of that statin should be continued. In this case, the dosage adjustment recommendations for that statin should be consulted.

Co-administration with ion exchange resins: Dosing of EZETROL should occur either ≥ 2 hours before or ≥ 4 hours after administration of an ion exchange resin.”

Special populations: see SPC

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

C : Cardiovascular system
C10 : Lipid-lowering agents
C10A : Cholesterol-lowering and triglyceride-lowering agents
C10AX : Other lipid-lowering agents
C10AX09 : Ezetimibe

2.2. Medicines in the same therapeutic category

In the same category there is no other inhibitor of intestinal absorption of cholesterol and phytosterols.

2.3. Medicines with a similar therapeutic aim

These are the other proprietary products indicated in the treatment of dyslipidaemias that are not controlled by statins or in cases of intolerance of these:

- cholestyramine: QUESTRAN,
- nicotinic acid: NIASPAN.

And all other lipid-lowering agents: fibrates.

3. SUMMARY OF THE TRANSPARENCY COMMITTEE'S OPINIONS

Opinion of the Committee of 12 and 26 November 2003

ACB: For most patients with hypercholesterolaemia, the therapeutic needs are theoretically covered by the use of statins. EZETROL, which as the dossier stands has not shown a clinical benefit in terms of morbidity/mortality, must at present be regarded as a second-line therapy.

The actual benefit of this proprietary product is substantial.

IAB:

- o In patients with primary hypercholesterolaemia who are not controlled with a statin alone: IAB III because of better tolerance in comparison with cholestyramine
- o In patients with primary hypercholesterolaemia in whom statin therapy is inappropriate or not well tolerated: IAB III in comparison with cholestyramine.
- o In combination with a statin, in cases of homozygous familial hypercholesterolaemia: IAB III in comparison with cholestyramine
- o In cases of homozygous sitosterolaemia: IAB II

4. UPDATING OF AVAILABLE DATA SINCE THE PREVIOUS OPINION

In support of its request, the company submitted 66 literature references, 48 of which are clinical studies.

Only new studies which have appeared since EZETROL's inclusion (opinion of 26 November 2003) and which concern clinical endpoints in terms of morbidity/mortality or vascular disease (surrogate endpoint) and/or safety will be examined in this opinion.

Data on the conditions of use of these proprietary products will also be presented and analysed.

4.1. **Efficacy**

Only comparative, randomised, controlled studies versus placebo or active treatments will be discussed in this opinion. Abstracts are excluded.

4.1.1. Studies of lipid parameters

The aim of most of the studies submitted by the company was to evaluate the effect of ezetimibe in combination with a statin on laboratory parameters (LDL-C levels) in various patient populations:

- The EASE¹ study, which evaluated the efficacy of adding ezetimibe to statin therapy in comparison with the statin alone in terms of the reduction of LDL-C levels in 2908 hypercholesterolaemia patients who were monitored for 6 weeks.
- The Stein 2004² study, which evaluated the efficacy of adding ezetimibe to atorvastatin therapy in comparison with atorvastatin alone in terms of the responder rates (percentage of patients with LDL-C $\leq$ 1 g/l) in 596 patients with a high cardiovascular risk who were not controlled who were monitored for 4 weeks.
- The Barrios 2005³ study, which evaluated the efficacy of the combination ezetimibe 10 mg/simvastatin 20 mg in comparison with atorvastatin 20 mg in terms of reduction of the LDL-C levels in 435 patients with a high cardiovascular risk who were not controlled by atorvastatin 10 mg and who were monitored for 6 weeks.
- The EASEGO⁴ study, which evaluated the combination ezetimibe 10 mg/simvastatin 20 mg in comparison with atorvastatin 20 mg and simvastatin 40 mg in terms of the responder rates (percentage of patients with LDL-C $\leq$ 1 g/l) in 367 patients with a high cardiovascular risk and/or type II diabetes who were not controlled by atorvastatin 10 mg or simvastatin 20 mg and who were monitored for 12 weeks.
- The Leiter 2008⁵ study, which evaluated the efficacy of the combination ezetimibe 10 mg/atorvastatin 40 mg in comparison with atorvastatin 80 mg in terms of the reduction of LDL-C levels in 556 patients with a high cardiovascular risk who were not controlled by atorvastatin 40 mg and who were monitored for 6 weeks.
- The Cruz-Fernandez 2005⁶ study, which evaluated the efficacy of the combination ezetimibe 10 mg/atorvastatin 10 or 20 mg (pooled results) in comparison with

¹ Pearson et al. "A community based, randomised trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL-c in hypercholesterolemic patients : the ezetimibe add-on to statin for effectiveness (EASE) trial" Mayo Clin Proc 2005;80(5):587-95.

² Stein et al. "Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: efficacy and safety of ezetimibe co-administered with atorvastatin" Am heart Journal, September 2004;148:447-55.

³ Barrios et al. "Lipid-altering efficacy of switching from atorvastatin 10 mg/day to ezetimibe/simvastatin 10/20mg/day compare to doubling the dose of atorvastatin in hypercholesterolaemic patients with atherosclerosis or coronary heart disease" Int J Clin Pract December 2005;59:1377-86.

⁴ Roeters et al. "The efficacy of statin monotherapy upitration versus switching to ezetimibe/simvastatin: result of the EASEGO study" Current medical research and opinion 2008;24:685-94.

⁵ Leiter et al. "Efficacy and safety of ezetimibe added on to atorvastatin (40 mg) compared with upitration of atorvastatin (to 80 mg) in hypercholesterolaemic patients at high risk of coronary heart disease" Am J Cardiol 2008;102:1495-501.

⁶ Cruz-Fernandez et al. "Efficacy and safety of ezetimibe co-administered with on-going atorvastatin therapy in achieving low-density lipoprotein goal in patients with hypercholesterolemia and coronary heart disease" Int J Clin Pract June 2005;59:619-27.

atorvastatin 10 or 20 mg (pooled results) in terms of the responder rates (percentage of patients with LDL-C ≤ 1 g/l) in 444 patients with coronary diseases who were not controlled by atorvastatin 10 or 20 mg and who were monitored for 6 weeks.

- The IN-CROSS study (Farnier 2009⁷), which evaluated the efficacy of the combination ezetimibe 10 mg/simvastatin 20 mg in comparison with rosuvastatin 10 mg in terms of the percentage reduction of LDL-C levels after 6 weeks' treatment in 618 hypercholesterolaemia patients with a high cardiovascular risk who were not controlled by a statin alone; the statin could be: atorvastatin 10 or 20 mg, fluvastatin 80 mg, pravastatin 40 mg, rosuvastatin 5 mg or simvastatin 20 or 40 mg.

These studies confirmed the efficacy of ezetimibe in combination with a statin (simvastatin, atorvastatin) for reduction of LDL-C (laboratory parameter). Insofar as they do not relate to the evaluation of clinical efficacy, these studies are not discussed in this opinion.

4.1.2. Studies of the impact on vascular disease (surrogate efficacy endpoint)

ENHANCE⁸ study

Method and objectives: Randomised, double-blind, comparative study of simvastatin 80 mg (n = 320) versus simvastatin 80 mg + ezetimibe (n = 322) which was carried out in 642 patients with familial hypercholesterolaemia and which aimed to evaluate the efficacy of ezetimibe in terms of progression of atherosclerosis after 24 months of treatment.

Inclusion criteria: adult patients between 30 and 75 years of age with familial hypercholesterolaemia and an LDL-C level ≥ 2.1 g/l on inclusion in the case of untreated patients or after the placebo run-in period in the case of patients previously treated with a cholesterol-lowering agent.

Primary endpoint: mean change (mm) in carotid intima-media thickness (IMT) after 24 months' treatment in comparison with baseline.

Secondary endpoints, including: change in the LDL-C level after 24 months' treatment in comparison with baseline.

Results: Intention-to-treat analysis (LOCF)

The characteristics of the patients on inclusion were comparable overall, except that the BMI was higher in the simvastatin + ezetimibe group (27.4 ± 4.6 versus 26.7 ± 4.4 , $p = 0.047$).

On inclusion, the IMT was 0.69 ± 13 mm and 0.70 ± 13 mm in the simvastatin + ezetimibe group and the simvastatin-only group respectively.

Statistically, after 24 months of treatment, there was no difference in the mean change in the carotid IMT (primary endpoint) in the two groups: 0.0111 ± 0.0038 mm in the simvastatin + ezetimibe group versus 0.0058 ± 0.0037 mm in the simvastatin-only group, difference 0.0053 mm, NS. A statistically significant reduction of LDL-C levels was observed in the simvastatin + ezetimibe group in comparison with the simvastatin-only group: -55.6 ± 0.9 mg/l versus -39.1 ± 0.9 mg/l, $p < 0.01$.

Conclusion

The addition of ezetimibe to high-dose simvastatin (80 mg) in patients with familial hypercholesterolaemia did not significantly reduce the IMT in comparison with simvastatin on its own, although LDL-C levels were significantly reduced. A correlation between lowering of LDL-C and the course of the atherosclerosis was not established in this study. The consequences of reduction of IMT (surrogate endpoint) in terms of the impact on morbidity/mortality are not yet established.

⁷ Franier et al. « Lipid-altering efficacy of ezetimibe/simvastatin 10/20 mg compared with rosuvastatin 10 mg in high risk hypercholesterolaemic patients inadequately controlled with prior statin monotherapy – The IN-CROSS study » Int J Clin Pract 2009.

⁸ Kastelstein et al. "Simvastatin with or without Ezetimibe in familial hypercholesterolemia", N. Engl. J. Med. April 3, 2008 358;14:1431-43.

SANDS⁹ study

The aim of this study was to compare the efficacy of "aggressive" treatment strategies (2 groups) consisting in reaching a target LDL-C value of 0.7 g/l with a standard strategy consisting in reaching a target LDL-C value of 1 g/l, in terms of change in IMT.

The aggressive strategies involved two groups: statin monotherapy (n = 154) and statin + ezetimibe (n = 69). The standard strategy was based on administration of a statin as monotherapy (n = 204).

As the benefit of "aggressive" strategies in terms of morbidity/mortality has as yet not been demonstrated, the results of this study are not discussed in this opinion.

4.1.3. Studies of morbidity/mortality

SEAS¹⁰ study

Method and objectives: Randomised, double-blind, comparative study of ezetimibe 10 mg + simvastatin 40 mg (n = 944) versus placebo (n = 929) which was carried out in 1873 patients with mild to moderate aortic stenosis and which aimed to evaluate the efficacy of the combination in terms of major cardiovascular events after 4 years of treatment.

Inclusion criteria: adult patients between 45 and 85 years of age with mild to moderate aortic stenosis evaluated by echocardiography.

Primary endpoint: percentage of patients with a major cardiovascular event (composite endpoint combining: cardiovascular mortality, aortic valve replacement, congestive heart disease, non-fatal myocardial infarction, hospitalisation because of unstable angina, coronary bypass, coronary angioplasty, and non-haemorrhagic CVA).

Results: Intention-to-treat analysis

After 4 years of treatment, there was no statistical difference between the percentages of patients with an observed cardiovascular event: 35.3% (333/944 patients) in the ezetimibe 10 mg + simvastatin 40 mg group versus 38.2% (355/929 patients) in the placebo group, HR 0.96 [0.83 – 1.12], NS.

Studies in progress:

Three other studies of morbidity/mortality are currently in progress: the MOBS, SHARP¹¹, and IMPROVE-IT¹² studies. The results of these studies are expected in 2010 (SHARP study) and 2013 (MOBS and IMPROVE-IT studies).

Pending the results of these three studies, the efficacy of EZETROL and INEGY has as yet not been demonstrated on the basis of a clinical, morbidity/mortality endpoint.

⁹ Fleg et al. "Effect of statins alone versus statins plus ezetimibe on carotid atherosclerosis in type 2 diabetes" J Am Coll Cardiol 2008;52:2198-205.

¹⁰ Rossebo et al. "Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis" New England Journal of Medicine September 2, 2008;359:1-14.

¹¹ Baigent et al. "Study of Heart and Renal Protection (SHARP)" Kidney International, Vol. 63, Supplement 84 (2003), pp. S207–S210

¹² Cannon et al. "Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): Comparison of ezetimibe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes" Am Heart J 2008;156:826-32.

4.2. Adverse effects

4.2.1. Tolerance data from the studies itemised above

ENHANCE study

In this study, 107/363 patients (29.5%) in the simvastatin-only group versus 122/357 patients (34.2%) in the ezetimibe + simvastatin groups showed adverse effects (the nature of the effects is not described in the publication).

The numbers dropping out because of adverse effects were comparable in the two groups: 34/363 (9.4%) versus 29/357 (8.1%).

SEAS study

During the 4 years of treatment, 854/943 patients (90.6%) in the ezetimibe 10 mg + simvastatin 40 mg group versus 852/929 patients (91.7%) in the placebo group showed adverse events.

Significant increases in ALAT and ASAT levels (> 3 times the normal limit) were observed in 16/925 patients (1.7%) of the ezetimibe 10 mg + simvastatin 40 mg group versus 5/915 (0.5%) of the placebo group, $p = 0.03$.

An increase in the incidence of cancer was also observed: 105/943 (11.1%) versus 70/929 (7.5%), $p < 0.01$.

4.2.2. Studies of safety

Peto study¹³

In this study the safety data from the three SEAS, SHARP, and IMPROVE-IT studies were pooled and reanalysed. In view of the multiplicity of hypotheses tested, the conclusions can be considered as being of an exploratory nature only. Furthermore, the events considered are rare events with "treatment" effects that are often non-significant and heterogeneous and are thus hard to interpret. Finally, the hypothesis of an effect of ezetimibe on the metastatic process was not tested.

Meta-analysis by Kashani 2008¹⁴

The aim of this meta-analysis was to evaluate the safety profile of the ezetimibe + statin combination in comparison with statin monotherapies.

Randomised double-blind studies versus statin monotherapy which were carried out in adult hypercholesterolaemia patients (at least 100 patients per group) and which were published between 1966 and 2006 were selected.

On the basis of these criteria, 18 studies in which adverse effects were reported were used for the analysis ($n = 14,471$).

Results:

Myalgia: myalgia was reported in 7/18 studies ($n = 3185$). There was no statistical difference in the frequency of myalgia in the treatment groups:

- Ezetimibe/statin combination versus statin alone: RR 0.86, 95% CI [0.60; 1.66],
- Ezetimibe versus statin: RR 0.32, 95% CI [0.06; 1.66].

Increases in CPK: increases in CPK were reported in 7/18 studies ($n = 5611$). There was no statistical difference in the frequency of these increases in the treatment groups:

- Ezetimibe/statin combination versus statin alone: RR 0.84, 95% CI [0.10; 6.81],
- Ezetimibe versus statin: RR 3.20, 95% CI [0.20; 50.50].

¹³ Peto et al. "Analyses of cancer data from three ezetimibe trials" N Engl J Med 2008;359:1-10.

¹⁴ Kashani et al. "Review of side-effect profile of combination ezetimibe and statin therapy in randomized clinical trials" Am J cardiol 2008;101:1606-13.

Rhabdomyolysis: rhabdomyolysis was reported in the 18 studies (n = 14,471). There was no statistical difference in the frequency of rhabdomyolysis in the treatment groups:

- Ezetimibe/statin combination versus statin alone: RR 0.67, 95% CI [0.27; 1.70],
- Ezetimibe versus statin: RR 0.97, 95% CI [0.20; 4.60].

Increases in transaminases: increases in transaminases were reported in the 18 studies (n = 14,471). There was no statistical difference in the frequency of these increases in the treatment groups:

- Ezetimibe/statin combination versus statin alone: RR 1.55, 95% CI [0.99; 2.44],
- Ezetimibe versus statin: RR 0.74, 95% CI [0.19; 2.88].

Gastrointestinal disorders: These disorders were reported in 7/18 studies (n = 3981) and were the most frequently reported adverse effect. There was no statistical difference in their frequency in the treatment groups:

- Ezetimibe/statin combination versus statin alone: RR 1.07, 95% CI [0.82; 1.38],
- Ezetimibe versus statin: RR 1.14, 95% CI [0.62; 2.10].

Conclusion: The authors concluded that there was no statistical difference, in terms of the frequency of the adverse effects reported in these studies (myalgia, increases in CPK and transaminases, rhabdomyolysis, and gastrointestinal disorders), between ezetimibe on its own or in combination with a statin on the one hand and a statin on its own on the other.

4.2.3. Pharmacovigilance and PSUR

The latest available PSUR on exposure to ezetimibe covers the period from 17 April to 16 October 2008 and covers 1,544,670 patient-years, 18,310 of which are from exposure in the course of clinical trials.

During this period, 954 spontaneously reported side effects and 8 from clinical trials were notified; 314 of them were considered serious.

The most frequently observed effects were:

- "musculoskeletal disorders" (myalgia): 33.4%,
- "investigations" (increases in CPK and ASAT/ALAT): 24.3%,
- "general disorders" (tiredness, asthenia, pain, malaise): 20.4%,
- "gastrointestinal disorders" (diarrhoea, nausea, pancreatitis): 18%.

With regard to the results of the SEAS study, a cumulative analysis of the cancer cases reported since 2003 was presented in the latest PSUR. Since 2003, 61 cancers/14,568,961 patient-years have been reported; of these, 21/1,554,670 patient-years were in 2008.

4.2.4. Changes to the SPC

Since 2003 the "undesirable effects" sections for the proprietary products have been modified in Marketing Authorisation amendments.

A section on the undesirable effects connected with the ezetimibe + fibrates combination has been added (see SPC). The data on the undesirable effects on laboratory parameters (increases in CPK and ASAT/ALAT) have likewise been expanded.

Finally, a section on the undesirable effects reported since marketing authorisation has been added:

- "Blood and lymphatic system disorders: thrombocytopenia
- Immune system disorders: hypersensitivity, including rash, urticaria, anaphylaxis, and angioedema
- Psychiatric disorders: depression
- Nervous system disorders: dizziness, paraesthesia
- Gastrointestinal disorders: nausea, pancreatitis
- Hepatobiliary disorders: hepatitis, cholelithiasis, cholecystitis

- Musculoskeletal and connective tissue disorders: arthralgia, myalgia; myopathy/rhabdomyolysis
 - Laboratory values: increase in transaminases; increase in CPK.”
- Because these adverse experiences have been identified from spontaneous reports, their true frequencies are not known and cannot be estimated.”

4.3. Conclusion

Efficacy:

The submitted studies, the aim of which was to evaluate the efficacy of ezetimibe in combination with a statin versus the statin on its own in terms of the reduction of LDL-C levels, confirm the efficacy of the combination of ezetimibe with a statin versus a statin alone, which was observed in the studies considered in the Transparency Committee's previous opinions.

In the ENHANCE study, after 24 months of treatment, there was no statistical difference in the mean change in the carotid IMT (primary endpoint) in the two groups compared: 0.0111 ± 0.0038 mm in the simvastatin + ezetimibe group versus 0.0058 ± 0.0037 mm in the simvastatin-only group, difference 0.0053 mm, NS. The addition of ezetimibe to high-dose simvastatin (80 mg) in patients with familial hypercholesterolaemia did not significantly reduce the IMT in comparison with simvastatin on its own, although LDL-C levels were significantly reduced. A correlation between lowering of LDL-C and the course of the atherosclerosis was not established in this study. The consequences of reduction of IMT (surrogate endpoint) in terms of the impact on morbidity/mortality are not yet established.

In the SEAS study, after 4 years of treatment, no statistically significant difference in the percentage of patients with a cardiovascular event was observed in the ezetimibe 10 mg/simvastatin 40 mg group in comparison with the placebo group: 35.3% (333/944 patients) versus 38.2% (355/929 patients), HR 0.96 [0.83 – 1.12], NS.

In these studies, the efficacy of ezetimibe in combination with a statin was demonstrated using a surrogate endpoint, LDL-C. Pending the results of the SHARP (2010), MOBS, and IMPROVE-IT (2013) studies, the efficacy of ezetimibe in combination with a statin has as yet not been demonstrated on the basis of a clinical, morbidity/mortality endpoint.

Safety:

In the ENHANCE study, adverse effects and dropouts were comparable in the two treatment groups – ezetimibe versus ezetimibe + simvastatin.

In the SEAS study, after 4 years of treatment, the most frequent adverse effects were:

- significant increases in ALAT and ASAT levels (> 3 times the normal limit): 1.7% in the ezetimibe 10 mg + simvastatin 40 mg group versus 0.5% in the placebo group, $p = 0.03$,
- an increase in the incidence of cancer: 11.1% in the ezetimibe 10 mg + simvastatin 40 mg group versus 7.5% in the placebo group, $p < 0.01$.

The meta-analysis by Kashani, which included 18 studies, concluded that the safety profile of the combination of ezetimibe + statin is comparable to that of statin monotherapies in terms of myalgia, increases in CPK and transaminases, rhabdomyolysis, and gastrointestinal disorders.

In the latest available PSUR (period from 17 April to 16 October 2008), the most frequently reported adverse effects were: musculoskeletal disorders (33.4%), increases in CPK and ASAT/ALAT (24.3%), general disorders such as tiredness, asthenia, pain, and malaise (20.4%), and gastrointestinal disorders such as diarrhoea, nausea, and pancreatitis (18%).

5. DATA ON THE USE OF THE MEDICINE

IMS-EPPM data

According to DOREMA data (IMS-EPPM, moving total to August 2008), a total of 347,000 prescriptions were issued for EZETROL.

EZETROL was prescribed to patients with abnormalities of lipid metabolism in 73% of cases and to patients with acute myocardial infarction in 2.6% of cases.

The prescriptions of these proprietary products are issued in the context of long-term therapy (mean duration: 70 days) at a mean dosage of 1 tablet per day.

Analysis of the conditions of use (see Annexe)

Following the Transparency Committee's request for a study in its opinion of 26 November 2003, the company provided the results of an observational study and of an *ad hoc* survey into the conditions of use of ezetimibe.

A cross-sectional descriptive observational study undertaken in 1200 general practitioners (Thalès panel) was instituted. Two sources of data from the Thalès monitoring centre are used: firstly, data from information collected routinely in the Thalès medical database over a period of 12 months (between January 2007 and December 2007), and secondly, data collected in an *ad hoc* survey undertaken among general practitioners on the Thalès panel (between 3 October 2006 and 31 December 2007), using on-line questionnaires that are triggered automatically and immediately after prescription of EZETROL or INEGY.

In the observational study, 912 doctors prescribed ezetimibe to 3440 patients, 1123 of whom received EZETROL alone and 2317 of whom received a statin/ezetimibe combination (1905 in the form of INEGY). In these patients, the percentages of men, diabetics, and patients with HDL cholesterol < 1 mmol/l are higher among the patients on a statin/ezetimibe combination, whilst the percentage of prescriptions for primary prevention purposes is higher among the patients given EZETROL alone. Age, hypertension, and diabetes are the most frequent cardiovascular risk factors. The percentages of men and of treatments prescribed for secondary prevention purposes are higher among the patients on ezetimibe than among the other patients treated with other lipid-lowering agents. In 61.6% of cases ezetimibe was prescribed in combination with 1 statin as second-line therapy – INEGY being prescribed in 1736 of these instances; in 32.6% of cases ezetimibe was prescribed as monotherapy and in 5.8% of cases it was prescribed in combination with 1 statin as first-line therapy. Prescription of INEGY often replaced that of a statin with which EZETROL can be combined; however, combination of INEGY with a statin was found in 79 patients.

The data from the *ad hoc* survey come from on-screen questionnaires completed by 285 doctors on the THALES panel. There are numerous missing data in this survey. Consequently, the results, which come from only 818 patients (418 given EZETROL alone and 400 given ezetimibe in combination) out of a total 2827 on-screen questionnaires triggered, do not relate to a population of patients and of doctors who are representative of the initial panel. In this study, the level of compliance with the Marketing Authorisation is 76.6% on EZETROL alone, 83.9% on INEGY, and 90.4% on EZETROL + statin. All of the results from the studies are presented in the annexe.

In addition, the study of morbidity/mortality which was also requested is currently in progress (protocol validated on 12 February 2008). The results will be available in 2011.

6. TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Reassessment of actual benefit

The cardiovascular diseases promoted by hypercholesterolaemia can be life-threatening.

The efficacy/adverse effects ratio for EZETROL is moderate.

The proprietary product falls under the category of preventive therapy.

The efficacy of ezetimibe was demonstrated on the basis of laboratory parameters only. For most patients with hypercholesterolaemia, the therapeutic needs are theoretically covered by the use of statins. EZETROL, which as yet has not shown a clinical benefit in terms of morbidity/mortality, must be regarded as a second-line therapy.

For patients who are insufficiently controlled by statins or who cannot tolerate them, there are treatment alternatives: nicotinic acid, cholestyramine, fibrates.

Public health benefit:

Cardiovascular diseases promoted by hypercholesterolaemia represent a major burden. For most patients with hypercholesterolaemia, the therapeutic needs are theoretically covered.

According to the clinical data available at present the proprietary product EZETROL lowers the level of LDL-C, but in the absence of data on morbidity/mortality the impact of the proprietary product EZETROL cannot be evaluated.

Consequently, it has not been demonstrated that the proprietary product EZETROL will benefit public health.

The actual medical benefit of EZETROL remains substantial.

6.2. Reassessment of the improvement in actual benefit (IAB)

In patients with primary hypercholesterolaemia who are not controlled by a statin alone, EZETROL in combination with statins provides a minor improvement in actual benefit (IAB IV) in the therapeutic strategy.

In patients with primary hypercholesterolaemia in whom statin therapy is contraindicated or not tolerated, in the absence of data on morbidity/mortality, EZETROL provides a minor improvement in actual benefit (IAB IV) in the therapeutic strategy.

In homozygous familial hypercholesterolaemia, EZETROL in combination with a statin provides a moderate improvement in actual benefit (IAB III) in comparison with cholestyramine.

In homozygous sitosterolaemia, EZETROL provides an important improvement in actual benefit (IAB II).

6.3. Therapeutic use

Standard therapeutic strategy

Hypercholesterolaemia must be managed in accordance with the AFSSAPS 2005¹⁵ recommendations currently in force. Treatment measures are guided by LDL-C thresholds, which differ according to the level of the patient's cardiovascular risk.

In dyslipidaemia patients who are not controlled by a statin alone, continuation and reinforcement of lifestyle and dietary measures (reduction of fat consumption, physical exercise) and the management of other risk factors, smoking in particular, are the first strategy to be implemented.

It is then necessary to check that the patient is correctly informed regarding his potential cardiovascular risk and that he is following the treatment properly. This is because poor compliance is the prime cause of non-achievement of the therapeutic targets.

If statin therapy is taken regularly at an appropriate dosage and dyslipidaemia is not controlled, the prescriber can add cholestyramine or ezetimibe.

In combination with a statin in cases where the effect on the lowering cholesterol is insufficient, nicotinic acid could be an alternative to cholestyramine or ezetimibe. Nevertheless, there is currently no study available that compares these medicines directly.

The lowering of serum LDL-C concentrations is a surrogate endpoint for the efficacy of cardiovascular prevention by lipid-lowering agents. When a combination of lipid-lowering agents can be considered, the choice thereof depends on the lipid abnormality that remains under monotherapy:

- for lowering LDL-C, the combinations statin+ezetimibe and statin+cholestyramine are possible;
- for influencing triglycerides and HDL-C, the combination statin+nicotinic acid is possible.

In dyslipidaemic patients in whom statin therapy is not tolerated, the prescriber currently has a choice of three medicines: fibrates, cholestyramine, ezetimibe. Fibrates are the drugs of preference in mixed dyslipidaemia with elevation of LDL-C and triglycerides and decreased HDL-C, whereas cholestyramine and ezetimibe would be the drugs of preference in pure hypercholesterolaemia.

Place of EZETROL

In the light of the available data, in the absence of data on morbidity/mortality, prescription of EZETROL in combination with statins must be reserved for second-line therapy of patients who are not adequately controlled (far from the LDL target) by a statin alone.

Prescription of EZETROL monotherapy must be restricted to patients in whom a statin is contraindicated or is not tolerated.

6.4. Target population

1. In patients with primary hypercholesterolaemia who are not controlled with a statin alone

The target population of EZETROL in combination with a statin is those people who do not achieve the therapeutic targets in spite of appropriate treatment with the currently available statins and in spite of good compliance with the treatment.

According to the Thalès panel data, around 5.3 million patients were treated with a statin in 2007.

Of these patients, a maximum of 35%, or 1.8 million people, do not currently achieve the treatment targets (all dosages together).

According to the various studies and data available, around 50% of patients treated with a statin are non-compliant. If patients who have not reached the therapeutic targets because of poor compliance with statin therapy are excluded, the target population of EZETROL would be at most 900,000 people.

¹⁵ « Prise en charge thérapeutique du patient dyslipidémique » Afssaps recommendations, March 2005.

2. In patients with primary hypercholesterolaemia in whom statin therapy is inappropriate or not well tolerated

Statin therapy is inappropriate or not well tolerated in approximately 1.1% of cases. Evidently 1% of patients show non-severe¹⁶ adverse effects and 0.1% show severe¹⁷ adverse effects.

Bearing in mind that the 5.3 million patients treated with statins represent the 99% of patients in whom a statin is justified, appropriate, and well tolerated, the target population in this indication would be around 58,000 patients.

3. In combination with a statin in patients with homozygous familial hypercholesterolaemia

The incidence of homozygous familial hypercholesterolaemia is reported to be 1 case per million births. As the life expectancy of these patients is lower than the mean life expectancy of the population, the target population in this indication would probably not exceed 50 patients.

6.5. Transparency Committee recommendations

The Transparency Committee recommends renewal of the inclusion of EZETROL box of 28 on the list of medicines reimbursed by National Health Insurance.

Packaging: Boxes of 28: not appropriate for the prescription conditions

The Committee points out that in accordance with its decision of 20 July 2005 it recommends that pack sizes for one-month treatments be harmonised as 30-day packs.

Reimbursement rate: 65%

¹⁶ Thompson et al. « Statin associated myopathy » JAMA, April 2, 2003 :vol 289 :1681-90.

¹⁷ Bruckert et al. « Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients – the PRIMO study » Cardiovascular Drugs therapy 2006, 19, 403-14.

ANNEXE

PUBLIC-HEALTH-INTEREST GROUP'S OPINION **ON THE PRELIMINARY RESULTS OF THE POST-LISTING STUDY OF EZETROL®/INEGY®**

PROTOCOL: Observational study of the conditions of introduction of treatment with EZETROL (ezetimibe) and INEGY (ezetimibe+ simvastatin) in non-hospital medical practice

VERSION : Preliminary report (2007), April 2008 version

PROPRIETARY PRODUCT: EZETROL/INEGY

COMPANY: MSD

DATE OF OPINION: 01/07/2008

I. SUMMARY OF THE REQUEST

A study was requested by the Transparency Committee in its opinion of 26 November 2003. The wording is as follows:

"The Committee wishes to have the results of a patient monitoring study, for the following in particular:

- the prescription conditions, the indications, and the associated treatments,
- the achievement of the treatment targets."

This request for a study was included in the CEPS [Committee for the Pricing of Healthcare Products] agreement of 06.12.04. The wording is as follows:

"The company undertakes to carry out an epidemiological study in a representative population of patients treated with Ezetrol®, under real-life prescription conditions and over the long-term. This study must make it possible:

- to describe, in the short-term, the prescription details (indications, coprescriptions) and the patients treated (sociodemographic data, patient history, disease history, particularly previous treatments),
- to describe, in the short-term, the treatment strategy and the use of healthcare services,
- to evaluate, in the long-term, the impact of this medicine on the health of the population concerned in terms of morbidity/mortality and safety (endpoints to be defined by the scientific committee)."

In its opinion of 21.09.05 on INEGY (ezetimibe + simvastatin), the Transparency Committee instructed the company to extend the study requested in patients treated with EZETROL to patients treated with INEGY.

II. REMARKS ON THE METHODOLOGY USED

The instituted study is a cross-sectional descriptive observational study undertaken in 1200 representative general practitioners (Thalès panel) in Metropolitan France. The protocol for this study was validated by the public-health-benefit (PHB) group on 30.05.2006.

Two sources of data from the Thalès monitoring centre are used: firstly, data from information collected routinely in the Thalès medical database (BDD) over a period of 12 months (between January 2007 and December 2007), and secondly, data collected in an ad hoc survey undertaken among general practitioners on the Thalès panel (between 3 October 2006 and 31 December 2007), using on-line questionnaires that are triggered automatically and immediately after prescription of EZETROL or INEGY.

Comparison between 285 active doctors who took part in the ad hoc study and the 1200 Thalès database doctors shows statistically significant differences in all the parameters analysed: among the active doctors, there are more men, they are older and they monitor more patients treated with lipid-lowering agents and more patients treated with ezetimibe. They thus cannot be regarded as representative of doctors in Metropolitan France (whilst conceding that the Thalès general practitioner database is representative of doctors in Metropolitan France). The rate of agreement to take part in the *ad hoc* study is low among the doctors and patients (23.7% and 18.5% respectively). In the absence of the reasons for the doctors' and patients' refusal to take part, their representativeness is not established. Other biases put a strain on the quality of the results:

- The exclusion, from the analysis, of patients who had not had a lipid profile in the preceding months;
- The large number of missing data, particularly in regard to the reasons for prescription.

All of these factors and their effect on the results should be discussed (sensitivity analysis).

The company did not respond to the PHB group's request that it provide the reasons for the doctors' refusal to take part in the study.

The results of this *ad hoc* study must therefore be treated with caution.

III. RESULTS PRESENTED

1. Analysis of the Thalès database in respect of the introduction of EZETROL and INEGY therapy

In total, 912 (76%) of the 1200 Thalès network doctors were initial prescribers of ezetimibe in 3440 patients, who were monitored regularly.

Of the 3440 patients whom the Thalès database listed as having been started¹⁸ on the treatment, 1123 (33%) received treatment with EZETROL alone and 2317 (67%) received treatment combining ezetimibe + statin (412 receiving EZETROL+ statin and 1905 receiving INEGY).

Male patients are more numerous in the ezetimibe-in-combination group (61.6%) than in the EZETROL only group (53.2%) ($p < 0.001$).

The patients treated with EZETROL alone are older (mean: 64.4 years) than the patients treated with ezetimibe in combination (62.6 years, $p < 0.0001$).

In the patients on EZETROL alone the treatment is more often given for primary prevention than in the patients on ezetimibe in combination (73.5% versus 60.2%, $p < 0.001$).

The dyslipidaemia-associated cardiovascular risk factors most frequently encountered in the patients on ezetimibe alone or in combination, irrespective of the type of prevention, are age over 50 years in men and 60 years in women (78.1% of cases), hypertension (56.7%), and diabetes (22.7%).

In the patients treated with EZETROL on its own there is a lower frequency of smoking (6.9% versus 13.6%), diabetes (17.2% versus 25.4%), and HDL cholesterol < 1 mmol/l (5.8% versus 9.5%) than in the patients treated with ezetimibe in combination with a statin.

In total, 13.9% of the patients on EZETROL on its own and 12.0% of the patients on ezetimibe in combination do not show any dyslipidaemia-associated risk factor, 31.8% and 29.8% show 1 associated risk factor, 37.9% and 35.3% show 2, and, finally, 16.4% and 22.9% show 3 or more of them ($p < 0.001$).

In comparison with the patients treated with other lipid-lowering agents:

- The percentage of men is higher in the ezetimibe (alone or in combination) group than in these patients taken as a whole (58.9% versus 54.6%, $p < 0.0001$);
- The patients treated with ezetimibe are younger than the patients receiving other lipid-lowering agents (63.2 years versus 64.8 years, $p < 0.0001$);
- In the patients treated with ezetimibe the treatment is more frequently given for secondary prevention than in the patients treated with other lipid-lowering agents (35.5% versus 25.3%, $p < 0.001$);
- Risk factors such as smoking (9.5% versus 7.7%) and HDL cholesterol < 1 mmol/l (9.5% versus 7.7%) are more frequent in the patients treated with ezetimibe;
- There is no statistically significant difference in regard to the distribution of the number of risk factors between patients on ezetimibe and patients on other lipid-lowering agents ($p = 0.3643$).

As regards the types of starting prescriptions, analysis of the data shows:

- 2118 patients (61.6%) received ezetimibe + statin as 2nd line therapy (50.5% INEGY and 11.1% EZETROL+ statin);
- 199 patients (5.8%) received ezetimibe + statin as 1st line therapy (4.9% INEGY and 0.9% EZETROL+ statin);
- 1123 (32.6%) received EZETROL alone (without a statin on the same prescription).

The reasons for prescription of EZETROL on its own after elimination of concomitant statin therapy were investigated in the ad-hoc study, the results of which are presented below.

Usually, the statin combined with EZETROL is Tahor® (28.6%), Crestor® (29.6%), or Elisor® (8.7%).

When INEGY is prescribed, it usually replaces these proprietary products and also Vasten®.

It may also be noted that INEGY was combined with a statin in 79 patients (2.3% of cases).

2. Analysis of the data from the ad-hoc survey (additional screens)

Out of the 798 doctors who agreed to take part in the study, 285 (36%) included patients, answering on-screen questionnaires that were triggered when ezetimibe was prescribed.

Statistically, these doctors differ significantly from the doctors on the Thalès panel on all of the parameters investigated:

¹⁸ I.e. no treatment with ezetimibe in the last 2 years.

- gender: there is a higher percentage of men (83.9% versus 78.3%, $p = 0.0227$);
- age: a higher percentage are in the over 51 age group (63.5% versus 53.4%, $p = 0.007$);
- number of patients treated with lipid-lowering agents and with ezetimibe: in 2007 they treated, on average, 146 patients with lipid-lowering agents and 12 patients with ezetimibe as opposed to 129 and 8 respectively for the Thalès panel doctors as a whole ($p < 0.001$).

Data for 818 patients were finally captured from 2827 triggered on-screen questionnaires: 418 patients were treated with EZETROL alone (51.1%) and 400 patients with ezetimibe in combination (48.9%).

The reasons provided to explain the difference between the 2827 on-screen questionnaires triggered and the 818 patients documented (difference = 2009 patients) are as follows:

- 522 (18.5%) of the on-screen questionnaires triggered related to patients who refused to take part in the study;
- 1375 (48.6%) of the on-screen questionnaires triggered actually related to a repeat prescription;
- 112 (4.0%) of the on-screen questionnaires triggered related to patients whose lipid profile was incomplete.

The patients included in the ad-hoc study were compared with the patients in the Thalès database, as a function of the treatment initiated (EZETROL on its own or ezetimibe in combination).

As regards the patients treated with EZETROL on its own, there is a statistically significant difference between them and the Thalès database patients in terms of the number of risk factors: the patients treated with EZETROL exhibit no (16.3% versus 13.9%) or only 1 (37.1% versus 31.8%) dyslipidaemia-associated risk factor more frequently than the Thalès database patients ($p = 0.0423$), there being no statistically significant difference in gender and age.

As regards the patients treated with ezetimibe in combination, there is a higher percentage of women (45% versus 38%, $p = 0.0122$). On the other hand, there is no difference in terms of age or the number of dyslipidaemia-associated risk factors.

In this study the 818 patients who were ultimately included comprised a higher percentage of men (54.8%) and had a mean age of 62.8 years (± 11.5). There is no statistically significant difference, in these parameters, between the patients treated with ezetimibe on its own and those treated with it in combination.

The analysis looked at 3 types of cardiovascular history: coronary disease, peripheral arterial occlusive disease (PAOD), and cerebrovascular accident (CVA), including transient ischaemic attacks. In most cases, the patients did not have any of these in their history and were regarded as patients treated for primary prevention (73.6% of cases).

In the secondary prevention cases (26.4%), the distribution of these 3 types of history was as follows: 19.2% showed coronary disease, 6.1% showed PAOD, and 3.9% showed a CVA. There was also a statistically significant difference according to whether ezetimibe was given on its own or in combination: the patients treated with ezetimibe in combination showed coronary disease (24.5% versus 14.1%) or PAOD (8.5% versus 3.8%) in a higher percentage of cases than the patients treated with EZETROL on its own, and they were thus treated for secondary prevention purposes in a higher percentage of cases (32.3% versus 20.8%, $p < 0.001$).

Turning to dyslipidaemia-associated risk factors, the most commonly reported were: age over 50 years for men and 60 years for women (72.2% of cases), hypertension (54.9%), and diabetes (24.2%). The two populations (EZETROL alone and ezetimibe in combination) differed according to the number of risk factors found: the proportion of patients with 2 associated risk factors and the proportion with at least 3 risk factors were higher in the patients treated with ezetimibe in combination (37.0% and 22.8% versus 31.8% and 14.8% respectively, $p = 0.001$).

In the case of almost all the patients (94.4%), the doctors stated that they had reminded their patients of the importance of diet, the percentage reminded being higher for ezetimibe in combination than for EZETROL on its own (97.0% versus 91.9%, $p < 0.001$).

The last lipid profile was done less than 3 months previously in 86.3% of cases and between 3 and 6 months previously in 7.5% of cases.

The total cholesterol level was on average 2.41 (± 0.56) g/l at the last profile performed and did not differ significantly between patients treated with EZETROL on its own and patients treated with ezetimibe in combination.

For LDL cholesterol and HDL cholesterol, the mean values at the last profile performed were 1.58 (± 0.49) g/l and 0.56 (± 0.16 g/l) respectively and differed significantly between patients treated with EZETROL on its own and those treated with ezetimibe in combination: 1.63 (± 0.50) and 1.53 ($\pm$

0.47) g/l for LDL cholesterol ($p = 0.0051$) and 0.57 (+/-0.16) and 1.54 (+/-0.15) g/l for HDL cholesterol ($p = 0.0326$).

Finally, the mean value for triglycerides was 1.54 (+/-1.00) g/l in the last lipid profile and likewise differed according to treatment type: 1.46 (+/-0.0125 g/l) in the patients treated with EZETROL on its own and 1.63 (+/-1.17) g/l in the patients treated with ezetimibe in combination ($p = 0.0125$).

In the case of the 418 patients treated with EZETROL on its own, the reason for prescription was not given in 64 instances (15.3%). Prescription of EZETROL on its own in this population was initiated because of:

- intolerance to statins in 305 patients (86.2% of the patients for whom a reason for prescription was reported and 72.9% of the total number of patients);
- a contraindication to statins in 15 patients (4.2% of the patients for whom a reason for prescription was reported and 3.6% of the total number of patients);
- another reason in 34 cases (9.6% of patients for whom a reason for prescription was reported and 8.1% of the total number of patients); a breakdown of these shows 11 cases of ineffective previous fibrate therapy, 2 cases of intolerance to fibrates, 14 cases of ineffective previous statin therapy, and 2 cases of ineffective previous therapy with a fibrate/statin combination.

If the wordings given in the Marketing Authorisation are followed, the indications for EZETROL on its own are adhered to in 76.6% of the patients treated (90.4% of the prescriptions for which a reason was reported): 305 patients with intolerance to statins and 15 patients in whom statins were contraindicated.

In the case of the 348 patients treated with INEGY, the reason for prescription was not given in 23 instances (6.6%). Prescription of INEGY in this population was initiated because of:

- insufficient control by statins on their own in 283 patients (87.1% of the patients for whom a reason for prescription was reported and 81.3% of the total number of patients);
- replacement of a statin therapy on account of intolerance in 24 patients (7.4% of the patients for whom a reason for prescription was reported and 7.4% of the total number of patients);
- replacement of EZETROL + statin therapy in 9 patients (2.8% of the patients for whom a reason for prescription was reported and 2.6% of the total number of patients);
- another reason in 9 cases (2.8% of the patients for whom the reason for prescription was reported or 2.6% of the total number of patients).

The indications for INEGY are thus adhered to *stricto sensu* in 83.9% of the patients treated (89.9% of the prescriptions for which a reason was reported).

In the case of the 52 patients in the EZETROL + statin group, the reason for prescription was given in all instances:

- 47 patients (90.4%) were not adequately controlled on statin therapy alone;
- In 5 patients (9.6%) previously prescribed a statin, there was a different reason (intolerance in 4 cases).

The Marketing Authorisation indications are thus adhered to in 90.4% of cases.

IV. CONCLUSION

Apart from the characteristics of the patients receiving ezetimibe which were described earlier (Thalès panel), it may be noted, from the results of the ad-hoc survey, that the reasons for prescription of ezetimibe are in line with those described in the Marketing Authorisation. The level of adherence to the Marketing Authorisation is 76.6% for EZETROL on its own, 83.9% for INEGY, and 90.4% for EZETROL + statin. Given the rate of doctor participation in this survey, however, the representativeness of these results is open to question (see Remarks on the methodology used).

In addition, the study of morbidity/mortality which was also requested is currently in progress (protocol validated on 12 February 2008). The results will be available in 2011.