HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

3 November 2010

TREDAPTIVE 1000 mg / 20 mg, modified-release tablet
B/28 (CIP code: 387 398-7)
B/28 (CIP code: 387 400-1)
B/49 (CIP code: 573 242-3)
B/56 (CIP code: 387 399-3)
B/56 (CIP code: 387 401-8)

Applicant: MSD CHIBRET

nicotinic acid/laropiprant
ATC code: C10AD52

List I

Date of Marketing Authorisation (centralised procedure): 8 July 2008

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance (boxes of 28 and 56) and approved for hospital use (boxes of 28, 49 and 56).

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredients
Nicotinic acid
Laropiprant

1.2. Background
A combination of nicotinic acid and laropiprant, a selective prostaglandin D2 receptor 1 inhibitor.

1.3. Indication
"TREDAPTIVE is indicated for the treatment of dyslipidaemia, particularly in patients with combined or mixed dyslipidaemia (characterised by elevated levels of LDL-cholesterol and triglycerides and low HDL-cholesterol) and in patients with primary hypercholesterolaemia (heterozygous familial and non-familial).

TREDAPTIVE should be used in patients, in combination with an HMG-CoA reductase inhibitor (statin), when the cholesterol-lowering effect of HMG-CoA inhibitor monotherapy is inadequate. It can be used as monotherapy only in patients who are intolerant to HMG-CoA reductase inhibitors, or in whom HMG-CoA reductase inhibitors are considered inappropriate or are not tolerated. Diet and other non-pharmacological treatments (e.g. exercise, weight reduction) should be continued during therapy with TREDAPTIVE."

1.4. Dosage
"The starting dose is one modified-release tablet (1000 mg nicotinic acid/20 mg laropiprant) once a day. After four weeks, it is recommended that patients be advanced to the maintenance dose of 2000 mg/40 mg taken as two modified-release tablets (1000 mg/20 mg each) once daily. Daily doses greater than 2000 mg/40 mg have not been studied and therefore are not recommended.

If TREDAPTIVE is interrupted for less than 7 consecutive days, patients can resume therapy at the last administered dose. If TREDAPTIVE is interrupted for 7 or more consecutive days, therapy should be resumed at the 1000 mg/20 mg dose for 1 week, before advancing to the maintenance dose of 2000 mg/40 mg.

Those patients switching from 2000 mg or more of prolonged-release nicotinic acid can initiate TREDAPTIVE at the 2000 mg/40 mg dose. Patients switching from less than 2000 mg of prolonged-release nicotinic acid should initiate therapy at the starting dose of 1000 mg/20 mg and if needed advance to the 2000 mg/40 mg maintenance dose after four weeks. For patients switching from immediate-release nicotinic acid to TREDAPTIVE, therapy should be initiated at the 1000 mg/20 mg dose and advanced to the 2000 mg/40 mg maintenance dose after four weeks.

The tablets should be taken whole, with food, in the evening or at bedtime. To preserve their modified-release properties, the tablets must not be split, broken, crushed, or chewed before swallowing. To reduce the possibility of flushing, drinking alcohol or hot drinks should be avoided at the time of ingestion of the medicinal product.

Use in the elderly: No dose adjustment is required for elderly patients.

Use in paediatric patients and adolescents: Tolerance and effectiveness of TREDAPTIVE in paediatric patients and adolescents have not been established. Therefore, treatment is not recommended in this age group.

Use in patients with hepatic or renal insufficiency: Use of TREDAPTIVE in patients with hepatic or renal insufficiency has not been studied. Like other nicotinic acid medicinal products,

TREDAPTIVE is contraindicated in patients with significant or unexplained hepatic dysfunction. It should be used with caution in patients with renal insufficiency, because nicotinic acid and its metabolites are primarily excreted by the kidneys.

Concomitant therapy: Acetylsalicylic acid provides no additional reduction of flushing beyond that achieved by TREDAPTIVE. Therefore, treatment with acetylsalicylic acid to alleviate flushing symptoms is not necessary. Because administration of bile acid sequestrants may reduce the bioavailability of acidic medicinal products such as nicotinic acid, it is recommended that TREDAPTIVE be administered more than 1 hour before or more than 4 hours after administration of a bile acid sequestrant. »

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

C	:	Cardiovascular system
C10	:	Hypolipidaemics
C10A	:	Cholesterol-lowering and triglyceride-lowering agents
C10AD	:	Nicotinic acid and derivatives
C10AD52	:	Nicotinic acid, combinations

2.2. Medicines in the same therapeutic category

These are the nicotinic-acid-based proprietary products indicated in the treatment of dyslipidaemia:

- in combination with an HMG-CoA reductase inhibitor (statin), when the cholesterol-lowering effect of HMG-CoA reductase inhibitor monotherapy is inadequate,
- as monotherapy in patients who cannot tolerate HMG-CoA reductase inhibitors (statins) or in whom statins are contraindicated:
  NIASPAN LP 350, 500, and 700 mg (nicotinic acid): in the process of being withdrawn from the market

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:

- QUESTRAN (cholestyramine),
- EZETROL (ezetimibe).

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The evaluation of the efficacy and tolerance of TREDAPTIVE is based on four controlled, randomised, double-blind, phase III studies in patients with primary hypercholesterolaemia or mixed dyslipidaemia.

The aim of these studies was to evaluate the effect of TREDPATIVE on lipid parameters and/or the effect on the occurrence of flush:

- Study P020: comparative study of TREDAPTIVE 1 g/20 mg x2/day versus NIASPAN 2 g/day versus placebo, carried out in 1387 patients followed up for 24 weeks,
- Study P022: factorial design, the aim of which was to compare the efficacy of the combination TREDAPTIVE 1 g/20 mg x2/day + simvastatin 20 or 40 mg (pooled) versus separate administration of these products, carried out in 1245 patients followed up for 8 weeks,
- Study P023: comparative study of TREDAPTIVE 1 g/20 mg x2/day with or without a preceding 5-day period without treatment versus NIASPAN 2 g/day, carried out in 681 patients followed up for 1 week,
- Study P054: comparative study of TREDAPTIVE 1 g/20 mg x2/day versus NIASPAN 2 g/day, carried out in 1449 patients followed up for 16 weeks.

Supplementary data added to the dossier:

- two expert opinions relating, on the one hand, to the link between HDL-c and cardiovascular risk and to the benefit of nicotinic acid and, on the other, to the pharmacological properties of laropiprant. As these opinions have not been published, they will not be discussed further in this opinion,
- a copy of a letter about a progress report on the ongoing morbidity/mortality trial (HPS2-THRIVE),
- the PSURs covering the period from May 2008 to May 2010,
- the tolerance data on TREDAPTIVE since it was first marketed (Finland 1/06/2009),
- an internal MSD summary on the effects of laropiprant submitted to the EMEA, which will not be taken into account in this opinion.
- the *post-hoc* analysis (Bays 2009[1]) of a study in which the principal aim was to evaluate the effect of TREDAPTIVE versus nicotinic acid (NIASPAN) alone on lipid parameters and flush. This *a posteriori* subgroup analysis compared the impact of these two treatments on the patients' blood pressure.
- a "proof-of-concept" study (Lai 2007[2]) concerning the effect of laropiprant on niacin-induced vasodilation of the skin, which, in view of its methodology, will not be examined in this opinion,
- the CHMP assessment which prompted a change to the SPC (25/01/2010), to incorporate the information on the increased incidence of myopathy observed in Asian patients in the HPS-THRIVE study.

1 Bays et al "Blood pressure-lowering effects of extended-release niacin alone and extended-release niacin/laropiprant combination : a post-hoc analysis of 24 week, placebo controlled trial in dyslipidemic patients" Clin Ther 2009;31:115-22.
2 Lai et al. "Suppression of niacin-induced vasodilatation with an antagonist to prostaglandin receptor subtype 1" Clin. Pharmacol. & therapeutics;81:849-57.

3.1.1. Study P020

Inclusion criteria: adult patients of 18 to 85 years of age with primary hypercholesterolaemia or mixed dyslipidaemia and:

- a triglyceride level ≤ 350 mg/l (3.95 mmol/l),
- an ALAT and ASAT level ≤ 1.5 times the normal limit,
- a creatine kinase level ≤ 2 times the normal limit,

Four categories of patients were included according to their level of cardiovascular risk defined according to the recommendations of the NCEP ATP III[3], but without stratification:

- patients treated with a statin and at high cardiovascular risk, with an LDL-c level < 1 g/l,
- patients treated with a statin and having more than two risk factors (RF), with an LDL-c level < 1.3 g/l,
- patients treated with a statin and at low cardiovascular risk (0 to 1 RF), with an LDL-c level of 1.3-1.9 g/l,
- patients not treated with a statin and at low cardiovascular risk, with an LDL-c level of 1.3-1.9 g/l.

Note: In this study, the patients selected had achieved the LDL-c goals prior to inclusion. The treatment of these patients with TREDAPTIVE is thus not justified from the viewpoint of the Marketing Authorisation, which specifies that TREDAPTIVE is to be used in combination with an HMG-CoA reductase inhibitor (statin) in patients in whom the cholesterol-lowering effect of HMG-CoA reductase inhibitor monotherapy is inadequate.

Treatments:

- TREDAPTIVE 1 g /20 mg x2/day, n = 696,
- NIASPAN 2 g/day, n = 434,
- placebo, n = 257.

After a 4-week period without a lipid-lowering agent, all the patients received TREDAPTIVE 1 g/ 20 mg/day or NIASPAN 1 g/day or placebo.
After these 4 weeks of treatment, the patients received TREDAPTIVE 1 g/20 mg x2/day or NIASPAN 2 g/day (forced titration) or placebo until the end of the study (12 weeks).

Note: In study P020, NIASPAN was administered at a dosage of 2g/day after 4 weeks' treatment with NIASPAN 1 g/day, which does not conform to the dose-escalation regimen recommended by the Marketing Authorisation, which specifies: “Therapy with NIASPAN must be initiated with a low dose and then increased according to the following regimen: week 1: 375 mg/day, week 2: 500 mg/day, week 3: 750 mg/day, week 4: 1 g/day, week 5: 1.5 g/day, week 6: 2 g/day. In addition, the "warnings section" specifies that "therapy with NIASPAN must be initiated in accordance with the dose-escalation regimen”; this dose regimen being recommended in order to reduce the occurrence of flush.

Primary endpoints:

- mean change (decrease) in the LDL-c level between weeks 12 and 24,
- maximum severity score for flush defined on the GFSS[4] scale evaluated once a day during the first week of treatment.

RESULTS: FSA[5] (full set analysis: defined as the set of patients who used the treatment and for whom at least one result is available) (see Tables 1 and 2).

3 National Cholesterol Education Programme – Adult Treatment Panel III
4 Global Flushing Severity score = 10-point scale evaluating severity: 0 = absent, 1 to 3 = mild, 4 to 6 = moderate, 7 to 8 = severe, 10 = extreme.
5 Full Set Analysis : defined as all of the patients who used the treatment and for whom at least one result is available

Table 1: Mean change in the LDL-c level between weeks 12 and 24.

	TREDAPTIVE 1 g/20 mg x2/day n = 696	NIASPAN 2 g/day n = 434	Placebo n = 257
Mean change (mg/dl) [95% CI]	-18.9 [-21.0, -16.8]	-18.1 [-20.5, -15.6]	-0.5 [-3.3, 2.4]
Difference from placebo [95% CI]	-18.4 [-21.4, -15.4]	ND	
p versus placebo	< 0.001		

ND = no data

After 12 weeks' treatment (between week 12 and week 24), a decrease in the LDL-c level was observed with TREDAPTIVE in comparison with placebo: -18.9 mg/dl [-21.0, -16.8] versus -0.5 [-3.3, 2.4], difference -18.4 [-21.4, -15.4], $p < 0.001$.
In the absence of a statistical test comparing the NIASPAN and TREDAPTIVE groups, no conclusion can be drawn as regards the reduction of LDL-c with these proprietary products.

Table 2: Maximum severity score for flush defined on the GFSS[2] scale during the first week of treatment

	TREDAPTIVE 1 g/20 mg x2/day n (%)	NIASPAN 2 g/day n (%)	Placebo n (%)	p versus NIASPAN
None/mild (score of 0 to 3)	538 (68.5)	233 (44)	246 (93.9)	
Moderate (score of 4 to 6)	136 (17.4)	120 (22.7)	15 (5.7)	
Severe (score of 7 to 9)	80 (10.2)	135 (25.5)	1 (0.4)	
Extreme (score of 10)	27 (3.5)	41 (7.8)	0 (0.0)	
Total	781	529	262	p < 0.001

After a week of treatment, the severity of flush was significantly reduced with TREDAPTIVE in comparison with NIASPAN. Given the dose-escalation regimen used for NIASPAN in this study (doubling of the dose after 4 weeks' treatment), which does not conform to the Marketing Authorisation and which promotes the development of flush, these results must be interpreted with caution.

3.1.2. Study P022

Inclusion criteria: adult patients of 18 to 85 years of age with primary hypercholesterolaemia or mixed dyslipidaemia and:

- a triglyceride level ≤ 350 mg/l (3.95 mmol/l),
- an ALAT and ASAT level ≤ 1.5 times the normal limit,
- a creatine kinase level ≤ 2 times the normal limit.

Two categories of patients were included according to their level of cardiovascular risk defined according to the recommendations of the NCEP ATP III[1], without stratification:

- patients with several cardiovascular risk factors, with an LDL-c level of 1.3-1.6 g/l,
- patients at low cardiovascular risk (0 to 1 RF), with an LDL-c level of 1.3-1.9 g/l.

Note: In this study, the patients were included on the basis of LDL-c levels that were too low relative to target LDL-c levels laid down by the recommendations. The treatment of these patients with TREDAPTIVE was thus not justified from the viewpoint of the Marketing Authorisation, which specifies that TREDAPTIVE should be used in combination with an HMG-CoA reductase inhibitor (statin) in patients in whom the cholesterol-lowering effect of HMG-CoA inhibitor monotherapy is inadequate.

Treatments:
After a period of 4 weeks on placebo, the patients were randomised to the following seven groups: TREDAPTIVE 1 g/10 mg, TREDAPTIVE 1 g/10 mg + simvastatin 10 mg, TREDAPTIVE 1 g/10 mg + simvastatin 20 mg, TREDAPTIVE 1 g/10 mg + simvastatin 40 mg, simvastatin 10 mg, simvastatin 20 mg, simvastatin 40 mg.

After 4 weeks of active treatment (period 1), the doses were doubled (forced titration) except in the unchanged simvastatin 40 mg group and the TREDAPTIVE 1 g/10 mg + simvastatin 40 mg group, in which only the TREDAPTIVE dose was doubled (period 2).

Primary endpoint: mean change (decrease) in LDL-c after 8 weeks of treatment.

RESULTS: FSA[3] analysis (cf. Table 3).

Table 3: Mean change in the LDL-c level after 8 weeks of treatment

	TREDAPTIVE 1 g/20 mg x2/day + simvastatin 20 or 40 mg (pooled results) n = 520	TREDAPTIVE 1 g/20 mg x2/day n = 160	Simvastatin 20 or 40 mg (pooled results) n = 565
Mean LDL-c level (SD) on inclusion (mg/dl)	151.8 (16.2)	149 (14.6)	151.5 (16.8)
Mean LDL-c level (SD) after 8 weeks of treatment (mg/dl)	79.9 (35.4)	126 (26.8)	96.9 (27.8)
Mean decrease since inclusion [95% CI]	-47.9% [-50; -45.8]	-17% [-20.3; -13.6]	-37% [-39.1; -35]
Difference versus simvastatin	- 10.8 [-13.2; -8.4]		
p versus simvastatin	< 0.001	ND	

ND = no data

After 8 weeks' treatment, a greater decrease in the LDL level was observed with TREDAPTIVE 1 g/20 mg x2/day + simvastatin 20 or 40 mg than with simvastatin (20 and 40 mg) monotherapy: -47.9% [-50; -45.8] versus -37% [-39.1; -35], difference -10.8 [-13.2; -8.4], p < 0.001.

3.1.3. Study P023

Inclusion criteria: adult patients between 18 and 70 years of age:
- with an ischaemic cardiovascular disease being treated with a statin and with an LDL-c level < 1.3 g/l,
- with diabetes being treated with a statin and with an LDL-c level < 1.3 g/l,
- without diabetes with 2 or more RF being treated with statins and with an LDL-c level < 1.6 g/l,
- without diabetes with fewer than 2 RF being treated with statins whatever their LDL-c level and a TG level < 5 g/l.

Treatments:
- TREDAPTIVE 1 g/20 mg x2/day for 2 weeks, n = 57,
- TREDAPTIVE 1 g/20 mg x2/day for 1 week after 5 days without treatment, n = 309,
- NIASPAN 2 g per day for 1 week after 5 days without treatment, n = 325.

During the first 4 weeks the patients all received TREDAPTIVE 1 g/ 20 mg. During the next 4 weeks the patients received TREDAPTIVE 1 g/ 20 mg x2/day. One group of patients then continued the treatment with TREDAPTIVE 1 g /20 mg x2/day for 2 weeks. In the second treatment group, the patients first discontinued their treatment for 5 days and were then divided into two groups: NIASPAN 2 g/day or TREDAPTIVE 1 g/20 mg x2/day.

Note: In study P023, NIASPAN was administered at a dosage of 2g/day from the outset, which does not conform to the dose-escalation regimen recommended by the Marketing Authorisation, which specifies: “Therapy with NIASPAN must be initiated with a low dose and then increased according to the following regimen: week 1: 375 mg/day, week 2: 500 mg/day, week 3: 750 mg/day, week 4: 1 g/day, week 5: 1.5 g/day, week 6: 2 g/day. In addition, the "warnings section" specifies that "therapy with NIASPAN must be initiated in accordance with the dose-escalation regimen”; this dose regimen being recommended in order to reduce the occurrence of flush.

Primary endpoint: maximum severity score for flush defined on the GFSS[2] scale evaluated once a day during the first week of treatment.

RESULTS: FSA[3] analysis (cf. Table 4).

Table 4: Maximum severity score for flush defined on the GFSS[2] scale during the first week of treatment

	5 days without treatment then TREDAPTIVE 1 g/20 mg x2/day for 1 week n (%)	5 days without treatment then NIASPAN 2 g/day for 1 week n (%)	TREDAPTIVE 1 g/20 mg x2/day for 2 weeks n (%)
None/mild (score of 0 to 3)	217 (70.2)	192 (59.1)	47 (82.5)
Moderate (score of 4 to 6)	62 (20.1)	80 (24.6)	8 (14)
Severe (score of 7 to 9)	26 (8.4)	47 (14.5)	1 (1.8)
Extreme (score of 10)	4 (1.3)	6 (1.8)	1 (1.8)
Global p versus NIASPAN	0.002	-	-

After a week of treatment, the severity of flush was significantly reduced with TREDAPTIVE 1 g /20 mg x2/day in comparison with NIASPAN 2 g/day. Given the dose-escalation regimen used for NIASPAN in this study (doubling of the dose after 4 weeks’ treatment), which does not conform to the Marketing Authorisation and which promotes the development of flush, these results must be interpreted with caution.

3.1.4. Study P054

Inclusion criteria: adult patients between 18 and 80 years of age:

- with an ischaemic cardiovascular disease being treated with statins and with an LDL-c level < 1.3 g/l,
- with diabetes being treated with statins and with an LDL-c level < 1.3 g/l,
- without diabetes with 2 or more RF being treated with statins and with an LDL-c level < 1.6 g/l,
- without diabetes with fewer than 2 RF being treated with statins whatever their LDL-c level and a TG level < 5 g/l.

Treatments:

- TREDAPTIVE 1 g/20 mg x2/day, n = 722,
- NIASPAN 2 g/day, n = 727.

After a 2-week washout, the patients received:

- TREDAPTIVE 1 g/20 mg for 4 weeks, then TREDAPTIVE 1 g/20 mg x2/day until the end of the study (12 weeks),
- NIASPAN 0.5 g/day for 4 weeks, after which the daily doses were increased in increments of 0.5 g every 4 weeks until a dose of 2 g /day was reached.

Note: In this study, NIASPAN was not administered in accordance with the dose-escalation regimen recommended by the Marketing Authorisation, which specifies that “therapy with NIASPAN must be initiated with a low dose and then increased according to the following regimen: week 1: 375 mg/day, week 2: 500 mg/day, week 3: 750 mg/day, week 4: 1 g/day, week 5: 1.5 g/day, week 6: 2 g/day”.

Primary endpoint: number of days per week with a maximum severity score for flush of moderate to extreme (GFSS[2] ≥ 4) over the 16 weeks of treatment.

RESULTS: FSA[3] analysis (cf. Table 5).

Table 5: Number of days per week with a maximum severity score for flush of moderate to extreme (GFSS[2] ≥ 4) over the 16 weeks of treatment.

	TREDAPTIVE 2 g/40 mg N = 722 n (%)	NIASPAN 2 g per day N = 727 n (%)
0 days	337 (46.7)	160 (22)
0 to 0.5 days	204 (28.3)	247 (34)
0.5 days to 1 day	59 (8.2)	121 (16.6)
1 to 2 days	43 (6)	105 (14.4)
2 to 3 days	28 (3.9)	50 (6.9)
More than 3 days	51 (7.1)	44 (6.1)
Global p versus NIASPAN	< 0.001	-

After 16 weeks of treatment, the number of days per week with a maximum severity score for flush of moderate to extreme (GFSS[2] ≥ 4) was significantly decreased with TREDAPTIVE 2 g/40 mg per day in comparison with NIASPAN 2 g per day. Given the dose-escalation regimen used for NIASPAN in this study, which does not conform to the Marketing Authorisation, these results must be interpreted with caution.

In this study, after 16 weeks of treatment:

- 82.3% of the patients treated with TREDAPTIVE versus 72.6% of the patients treated with NIASPAN showed a GFSS score ≥ 4 at least 1 day per week,
- 46.7% of the patients treated with TREDAPTIVE versus 22% of the patients treated with NIASPAN did not show any flush.

3.1.5. Supplementary data added to the dossier: Bays 2009[6] study

Method: post-hoc analysis of study P020 described above. This *a posteriori* subgroup analysis compared the impact of TREDAPTIVE and of nicotinic acid (NIASPAN) alone on the (systolic and diastolic) blood pressure of patients included and followed up for 24 weeks.

Results:

After 24 weeks of treatment, a reduction in systolic and in diastolic blood pressure was observed compared to baseline:

- Systolic BP: -3.4 mm Hg [-4.6; -2.3] in the TREDAPTIVE group versus -2.5 mm Hg [-3.8; -1.2] in the NIASPAN group versus -0.3 mm Hg [-2; 1.4] in the placebo group (no statistical test performed).
- Diastolic BP: -2.1 mm Hg [-2.8; -1.3] in the TREDAPTIVE group versus -2.3 mm Hg [-3.1; -1.4] in the NIASPAN group versus 0.4 mm Hg [-0.7; 1.5] in the placebo group (no statistical test performed).

The methodology of this (*a posteriori* subgroup) analysis gives the results an exploratory character. These need to be confirmed by a study in which the primary objective is to determine the impact of these treatments on blood pressure. These results must therefore be interpreted with caution.

6 Bays et al "Blood pressure-lowering effects of extended-release niacin alone and extended-release niacin/laropiprant combination: a post-hoc analysis of 24 week, placebo controlled trial in dyslipidemic patients" Clin Ther 2009;31:115-22.

3.2. Adverse effects

Study 020
Tolerance was evaluated in 1609 patients. The proportion of patients who had at least one adverse effect was 29.8% (n = 480): 247 patients (31%) in the TREDAPTIVE group, 187 patients (34.6%) in the NIASPAN group, and 46 patients (17%) in the placebo group.

The most frequent adverse effects in the TREDAPTIVE, NIASPAN and placebo groups respectively were:
- flush: 60 patients (7.5%) versus 82 patients (15.2%) versus 5 patients (1.9%),
- diarrhoea: 21 patients (2.6%) versus 10 patients (1.8%) versus 1 patient (0.4%),
- nausea: 23 patients (2.9%) versus 11 patients (2.0%) versus 5 patients (1.9%),
- feeling hot: 21 patients (2.6%) versus 18 patients (13.3%) versus 2 patients (0.7%),
- paraesthesia: 23 patients (2.9%) versus 25 patients (4.6%) versus 3 patients (1.1%),
- pruritus: 45 patients (5.6%) versus 34 patients (6.3%) versus 6 patients (2.2%),
- increase in blood glucose levels: 28 patients (3.7%) versus 23 patients (4.4%) versus 2 patients (0.7%).

Study 022
Tolerance was evaluated in 1297 patients. The proportion of patients who had at least one adverse effect was 35.3% (n = 458): 258 patients (42.8%) in the TREDAPTIVE + simvastatin 20 or 40 mg group, 97 patients (49.7%) in the TREDAPTIVE monotherapy group, and 103 patients (17.4%) in the simvastatin 20 or 40 mg group.

The most frequent adverse effects were:
- flush: 107 patients (17.6%) versus 36 patients (18.5%) versus 4 patients (0.7%),
- diarrhoea: 20 patients (3.3%) versus 8 patients (4.1%) versus 13 patients (2.2%),
- nausea: 218 patients (3%) versus 11 patients (5.6%) versus 7 patients (1.2%),
- paraesthesia: 35 patients (5.7%) versus 8 patients (4.1%) versus 6 patients (1%),
- pruritus: 31 patients (5.1%) versus 15 patients (7.7%) versus 6 patients (1%).

Study 023
Tolerance was evaluated in 694 patients. In the treatment phase of this study (1 week), 33 patients (4.7%) showed at least one adverse effect: 9 patients (2.9%) in the “5 days without treatment/TREDAPTIVE group”, 24 patients (7.4%) in the “5 days without treatment + NIASPAN group”, and none in the TREDAPTIVE group.

The most frequent adverse effects were:
- flush: 3 patients versus 11 patients versus 0 patients,
- pruritus: 3 patients versus 6 patients versus 0 patients.

Study 054
Tolerance was evaluated in 1452 patients. In this study, 563 (38.7%) showed at least one adverse effect: 249 patients (24.3%) in the TREDAPTIVE group and 314 patients (43.2%) in the NIASPAN group.

The most frequent adverse effects were:
- flush: 97 patients (13.4%) versus 207 patients (28.5%),
- pruritus: 51 patients (7%) versus 52 patients (7.2%),
- paraesthesia: 21 patients (2.9%) versus 19 patients (2.6%),
- rash: 19 patients (2.6%) versus 15 patients (2.1%),
- nausea: 14 patients (1.9%) versus 5 patients (0.7%),
- feeling hot: 15 patients (2.1%) versus 14 patients (1.9%),

PSURs: May 2008 to May 2010:
The company submitted data from the PSURs covering an 18-month period between May 2008 and November 2009, during which over 12,000 patients were included in the studies (pivotal studies, postmarketing studies, compassionate-use programme). The cumulative severe adverse events observed were:

- cardiac disorders (2): unstable angina, pericarditis,
- gastrointestinal disorders (4): haemorrhagic gastritis, haematemesis, odynophagia, pancreatitis,
- hepatic disorders (5): acute cholecystitis, cholelithiasis, cirrhosis of the liver, and 2 cases of hepatitis,
- metabolic disorders (6): 5 cases of diabetes and one case of lactic acidosis,
- musculoskeletal disorders (25): 25 instances of myopathy,
- renal disorders (2): acute renal failure,
- respiratory disorders (1): respiratory shock
- skin disorders (1): erythema

In addition, PSUR 3 shows that over 17,000 patients were exposed to TREDAPTIVE between June 2009 and November 2009. In real life, no long-term data have been collected, the maximum duration for which patients have been treated being 5 months.
The events reported since the start of marketing of TREDAPTIVE were:

- cardiac disorders (5): MI, unstable or stable angina, coronary disease (2),
- gastrointestinal disorders (4): flatulence, cheilitis, labial or buccal oedema,
- metabolic disorders (2): increase or decrease in appetite,
- musculoskeletal disorders (3),
- renal disorders (2): renal pain and urinary problem,
- respiratory disorders (1): epistaxis,
- skin disorders (8): alopecia, vesicular rash (4), skin allergy, Stevens-Johnson syndrome,
- psychiatric disorders (3): agitation, nervousness, psychological instability,
- nervous disorders: hyperaesthesia,
- disturbances of laboratory parameters (3): increase in TG, gamma-GT, and decrease in HDL,
- ocular disorders (3): hyperaemia, orbital oedema, visual disturbance.

In the latest PSUR covering the period between November 2009 and May 2010, the cumulative severe adverse events observed were:

- cardiac disorders (2): unstable angina (1), pericarditis (1),
- gastrointestinal disorders (5): haemorrhagic gastritis, haematemesis, odynophagia, pancreatitis,
- hepatic disorders (6): cholecystitis, cholelithiasis, cirrhosis of the liver, hepatitis,
- metabolic disorders (6): diabetes (6) and lactic acidosis (1),
- musculoskeletal disorders (31): myopathy,
- renal disorders (2): acute renal failure,
- respiratory disorders (2): asthma
- skin disorders (2).

The preliminary data from the HPS-THRIVE study showed an increase in the incidence of myopathy cases in the patients included, particularly patients of Asian origin (mean incidence of 0.9% and of 0.43% in the randomised phase). The increase in this incidence relative to the incidences observed in the earlier studies (0.08%) is not explained and is in the process of being evaluated. Consequently, new studies have been instituted: a pharmacokinetics study and a genomic study in Asian patients.
A change to the TREDAPTIVE SPC, incorporating the information on myopathy, has been validated by the EMEA, however (SPC of 25/01/2010). In addition, the RMP was updated in August 2009 to take account of the myopathies observed in the HPS-THRIVE study but has not yet been evaluated by the EMEA.

3.3. Conclusion

The efficacy and tolerance of TREDAPTIVE were evaluated in four controlled, randomised, double-blind, comparative studies (studies P020, P022, P023, and P054) in patients with primary hypercholesterolaemia or mixed dyslipidaemia.

In study P020:
- After 12 weeks' treatment (between week 12 and week 24), a decrease in the LDL-c level was observed with TREDAPTIVE in comparison with placebo: -18.9 mg/dl [-21.0, -16.8] versus -0.5 [-3.3, 2.4], difference -18.4 [-21.4, -15.4], $p < 0.001$.

In the absence of a statistical test comparing the NIASPAN and TREDAPTIVE groups, no conclusion can be drawn as regards the reduction of LDL-c with these proprietary products.
- After a week of treatment, the severity of flush, evaluated on the GFSS scale, was significantly reduced with TREDAPTIVE in comparison with NIASPAN. Given the dose-escalation regimen used for NIASPAN (doubling of the dose after 4 weeks' treatment), which does not conform to the Marketing Authorisation and which promotes the development of flush, these results must be interpreted with caution.

In study P022, after 8 weeks of treatment, a decrease in the LDL-c level was observed with TREDAPTIVE + simvastatin 20 or 40 mg in comparison with simvastatin monotherapy: -47.9% [-50; -45.8] versus -37% [-39.1; -35], difference -10.8 [-13.2; -8.4], $p < 0.001$.

In study P023, after a week of treatment, the severity of flush, evaluated on the GFSS scale, was significantly reduced with TREDAPTIVE in comparison with NIASPAN. Given the dose-escalation regimen used for NIASPAN in this study (doubling of the dose after 4 weeks' treatment), which does not conform to the Marketing Authorisation and which promotes the development of flush, these results must be interpreted with caution.

In study P054, after 16 weeks of treatment, the number of days per week with a maximum severity score for flush of moderate to extreme ($GFSS^2 \geq 4$) was significantly decreased with TREDAPTIVE 1 g/20 mg x2/day in comparison with NIASPAN 2 g/day. Given the dose-escalation regimen used for NIASPAN in this study, which does not conform to the Marketing Authorisation, these results must be interpreted with caution.

The relevance of these results is hard to gauge in view of:
- the short durations of analysis of the results (one week in studies P022 and P023),
- the dosage regimen used for the comparator (NIASPAN), which does not conform to the Marketing Authorisation and is conducive to poor tolerability,
- the characteristics of the patients on inclusion:
  - patients selected who had achieved the LDL-c goals prior to inclusion, who do not conform to the Marketing Authorisation indication for TREDAPTIVE and the recommendations in force[7] (studies P020 and P022),
  - patients with primary hyperlipidaemia or mixed dyslipidaemia: however, according to the recommendations in force, a combination of statin+nicotinic acid can be offered to influence triglycerides and HDL-c, i.e. in mixed hyperlipidaemia.

The long-term tolerance and efficacy of TREDAPTIVE have not been investigated. Uncertainties over the potential impact of laropiprant in the long term persist in view of its action mechanism (prostaglandin inhibitor) and the high-cardiovascular-risk target population of this proprietary product.

7 "Prise en charge thérapeutique du patient dyslipidémique" [Therapeutic management of the dyslipidemic patient] (Afssaps [French Health Product Safety Agency] recommendations, March 2005.

Furthermore, there are no data available regarding the potential recurrence of flush in the long term after discontinuation of laropiprant. On the basis of the available data, the benefit of continuing this combination in the long term remains to be demonstrated.

The benefit of TREDAPTIVE in regard to morbidity/mortality has not been established.

No study versus another hypolipidaemic drug is available.

The adverse effects observed most frequently during these four studies (>1%) were: flush, pruritus, paraesthesia, feeling hot, diarrhoea, nausea.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

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

The short-term efficacy/adverse effects ratio of this product is moderate in this indication. The long-term efficacy/adverse effects ratio of this product in this indication has not been clearly established.

In the absence of morbidity/mortality data, this product falls under the category of symptomatic treatment for dyslipidaemia.

For most patients with dyslipidaemia, the therapeutic needs are theoretically covered by the use of statins. For patients who are insufficiently controlled by statins or who cannot tolerate them, there are treatment alternatives: nicotinic acid, ezetimibe, cholestyramine, fibrates.

TREDAPTIVE is a second-line therapy which must be used in combination with statins and reserved for hypercholesterolaemia patients who are not controlled by a statin alone and in whom lowering of triglycerides (TG) and raising of HDL cholesterol (HDL-c) is required (Afssaps [French Health Product Safety Agency] recommendations 2005)[7].

Public health benefit:

The cardiovascular diseases promoted by dyslipidaemias can be life-threatening and are common. The public-health burden of dyslipidaemia is thus a major one. It remains substantial in the subpopulations who may benefit from the treatment, as defined in the indication of the product.

Management of dyslipidaemia is a public-health need. However, the therapeutic need is covered by the treatments currently available, whether as monotherapy or as bitherapy.

On the basis of the available clinical trial data and in view of the existing therapies, it is not expected that the proprietary product TREDAPTIVE will have an additional impact on morbidity/mortality.

Furthermore, it is not certain that these results can be carried over into clinical practice in so far as the profile of patients treated may differ from that of the patients in the trials.

In addition, the long-term tolerance profile and efficacy of laropiprant is unknown.

Consequently, it is not expected that the proprietary product TREDAPTIVE will benefit public health.

In view of:

- the methodological shortcomings of the efficacy data from the studies provided in the dossier (short-term studies, comparator dosage regimen which does not conform to the Marketing Authorisation, treated patients who do not conform to the Marketing Authorisation indication and the recommendations in force), which make the results hard to interpret,
- the absence of long-term data on continued efficacy in regard to laboratory parameters on the one hand and tolerance on the other, particularly in regard to the action mechanism of laropiprant (prostaglandin inhibitor),
- the absence of demonstrated equivalence of efficacy versus NIASPAN,

the actual benefit of TREDAPTIVE in combination with statins is moderate in patients with hypercholesterolaemia who are not controlled by a statin alone and in whom lowering of TG and raising of HDL cholesterol is required.

4.2. Improvement in actual benefit (IAB)

TREDAPTIVE does not provide an improvement in actual benefit (IAB V) in the management of patients with mixed dyslipidaemia who are not controlled by statins alone.

4.3. Therapeutic use[8]

In dyslipidaemia patients, reduction of fat consumption, physical exercise, and the management of other risk factors, smoking in particular, are the first strategy which should be implemented and should be continued throughout the treatment.

Treatment measures are then guided by LDL-c thresholds, set according to the patient's cardiovascular risk and the tolerability of the treatments.

In patients who are not controlled by a statin alone, it is important to ensure that the information about the patient's cardiovascular risk is correct and understood and that the treatment is taken regularly. This is because poor compliance is the prime cause of non-achievement of the therapeutic targets. It is also necessary to ensure that the statin is prescribed at dosages that showed a clinical benefit in the various studies of morbidity/mortality.

If the dyslipidaemia remains uncontrolled in spite of treatment with a statin taken regularly at an appropriate dosage, cholestyramine or ezetimibe can be added.
In combination with a statin in cases where the effect on lowering of cholesterol is insufficient, nicotinic acid is an alternative to cholestyramine or ezetimibe.

The lowering of serum LDL-c concentrations is a surrogate endpoint for the efficacy of cardiovascular prevention by hypolipidaemics. When a combination of hypolipidaemics 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+resin can be considered,
- for influencing triglycerides and HDL-c, the combination statin+nicotinic acid is possible.

In cases of pure hypertriglyceridaemia, fibrates may be used if TG levels remain above 4 g/l.

Therapeutic use of TREDAPTIVE:
In view of:

- the methodological shortcomings of the efficacy data from the studies provided in the dossier (short-term studies, comparator dosage regimen which does not conform to the Marketing Authorisation, treated patients who do not conform to the Marketing Authorisation indication and the recommendations in force), which make the results hard to interpret,
- the absence of long-term data on its continued efficacy in regard to laboratory parameters on the one hand and its tolerance on the other, particularly in regard to the action mechanism of laropiprant (prostaglandin inhibitor),
- the absence of demonstrated equivalence of efficacy versus NIASPAN,

TREDAPTIVE must be reserved for patients with hypercholesterolaemia who are not controlled by a statin alone and in whom lowering of TG and raising of HDL-c is required (Afssaps [French Health Product Safety Agency] recommendations 2005).

4.4. Target population

The target population of TREDAPTIVE is patients with hypercholesterolaemia who are not controlled by statins alone and in whom lowering of triglycerides and raising of HDL cholesterol is required.

It can be estimated from the following data:

- According to the Thales-Cegedim panel data, around 5.35 million people were treated with a statin in 2007[8].

8 HAS. Efficacité et efficience des hypolipémiants : une analyse centrée sur les statines [Efficacy and efficiency of hypolipidaemics: a statin-centred analysis]. July 2010

- Of these patients, it seems that roughly 37%[9], or 1.98 million people, do not achieve the treatment targets for LDL cholesterol (all dosages together). According to the various studies and data available, around 60% of patients treated with a statin are non-compliant[10]. If patients who have not reached the therapeutic targets because of poor compliance with statin therapy are excluded, the target population of patients not controlled by a statin would be at most 790,000 people per year.
- According to the study by Ferrières et al. (2010)[10], of the patients treated with hypolipidaemics who do not achieve the therapeutic target for LDL cholesterol, 12.6% or around 99,000 patients have a high TG and low HDL-c level.

The target population of TREDAPTIVE in combination with statins in patients with hypercholesterolaemia who are not controlled by a statin alone and in whom lowering of triglycerides and raising of HDL cholesterol is required can thus be estimated at 99,000 patients.
As a rough guide, according to DOREMA data (IMS-EPPM, moving total May 2010), 12,000 prescriptions were issued for NIASPAN (nicotinic acid on its own).

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in combination with statins, in patients with hypercholesterolaemia who are not controlled by a statin alone and in whom lowering of triglycerides and raising of HDL cholesterol is required, at the dosage in the Marketing Authorisation.

Packaging: not appropriate for the prescription conditions.
The Committee points out that, for treatments lasting one month, it recommends harmonisation of the size of packs at 30 days' treatment, in accordance with its deliberations of 20 July 2005.

Reimbursement rate: 35%

9 Ferrières et al. Residual dyslipidemia after statin treatment in France: Prevalence and risk distribution. Archives of Cardiovascular Disease 2010; 103: 302 - 309
10 Johnson SS. Transtheoretical model intervention for adherence to lipid-lowering drugs. Dis Manag 2006 ;9(2):102-14.