HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

28 May 2008

PLETAL 50 mg, tablets
Box of 56 tablets, CIP code: 384 040-4

PLETAL 100 mg, tablets
Box of 56 tablets, CIP code: 384 058-0

Applicant: OTSUKA

cilostazol
ATC code: B01AC

List I

Date of Marketing Authorization: 12/02/2008
European marketing authorization (mutual recognition, reporting country UK).

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for hospital use.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Cilostazol

1.2. Indication

Pletal is indicated for the improvement of maximal and pain-free walking distances in patients with intermittent claudication, who do not have rest pain and who do not have evidence of peripheral tissue necrosis.

1.3. Dosage

The recommended dosage of cilostazol is 100 mg twice a day. Cilostazol should be taken 30 minutes before or two hours after breakfast and the evening meal. Taking cilostazol with food has been shown to increase the maximum plasma concentrations (C_{max}) of cilostazol, which may be associated with an increased incidence of adverse effects.
Treatment for 16-24 weeks can result in a significant improvement in walking distance. Some benefit may be observed following treatment for 4-12 weeks.

The elderly: There are no special dosage requirements for the elderly.

Children: Safety and efficacy in children have not been established.

Renal impairment: No dose adjustment is necessary in patients with a creatinine clearance of >25 ml/min. Cilostazol is contraindicated in patients with a creatinine clearance of ≤ 25 ml/min.

Hepatic impairment No dosage adjustment is necessary in patients with mild hepatic disease. There are no data in patients with moderate or severe hepatic impairment. Since cilostazol is extensively metabolized by hepatic enzymes, it is contraindicated in patients with moderate or severe hepatic impairment.

2 COMPARABLE MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

B : blood and blood-forming organs
B01 : antithrombotic agents
B01A : antithrombotic agents
B01AC : platelet aggregation inhibitors excluding heparin

2.2. Medicines in the same therapeutic category

Other platelet aggregation inhibitors indicated for patients with claudication:

- PLAVIX (clopidogrel)
- TICLID (ticlopidine)

2.3. Medicines with a similar therapeutic aim

Peripheral vasodilators *(low AB*) :

- FONZYLANE (buflomedil) and generics,
- PRAXILENE (naftidrofuryl) and generics.

And medicinal products based on: Gingko biloba, ifenprodil, nicergoline, pentoxifylline, and piribedil *(insufficient AB).*

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The efficacy and safety evaluation of cilostazol (PLETAL) is based on:

- nine placebo-controlled clinical trials, three of which also included a pentoxifylline 400 mg group: 90-201[1], 92-202[2], 93-201[3], 94-201[4], 94-203[5], 94-301 (unpublished), 95-201 (unpublished),96-202 [6], PACE 98-213 (unpublished),
- a Cochrane Review[7] of eight of the nine trials (excluding the PACE trial 98-213*),
- a "pooled" analysis of the said nine placebo-controlled trials,
- a long-term trial (CASTLE trial[8]),

** unavailable when the Cochrane group's analysis was conducted.*

3.1.1. Placebo-controlled trials

The nine placebo-controlled trials were conducted with the same objectives and the same methodology.

Objective: To evaluate the efficacy of cilostazol (PLETAL) vs. placebo in patients with stable, moderate intermittent claudication (no pain at rest and no signs of peripheral tissue necrosis).

Methods: Randomized, double-blind, parallel-group, placebo-controlled trials. Trials 94-301, 96-202 and PACE 98-213 also included a pentoxifylline 400 mg control group.

Treatment (see tables 1 and 2). The treatment lasted 12 to 24 weeks:

- cilostazol 50, 100 or 150 mg twice daily
- pentoxifylline 400 mg three times daily,
- placebo

Inclusion criteria: Patients over 40 years old with:

- claudication for at least 24 weeks, and no significant change in symptoms in the 3 months prior to inclusion.
- peripheral occlusive arterial disease of the lower limbs defined as a ankle brachial index (ABI) ≤ 0.90 for 8 trials and ≤ 0.80 for one trial.

Non-inclusion criteria:

- maximal walking distance varying by over 20% during 2 or 3 consecutive tests on a treadmill,
- thromboangiitis obliterans,
- pain at rest attributed to ischaemia,
- ulcers, gangrene, ischaemic necrosis, surgery or endovascular intervention during the last 3 months,

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[1] Dawson et al. "Cilostazol has beneficial effects in treatments of intermittent claudication" Circulation 1998; 98: 678-686.

[2] Beebe et al. "A new pharmacological treatment for intermittent claudication: result of a randomized multicenter trial" Arch. Inter. Med 1999;159:2041-50.

[3] Elam et al. "Effect of a novel antiplatelet agent cilostazol on plasma lipoproteins in patients with intermittent claudication" Arterioscler Thromb Vasc Biol 1998;18:1942-7.

[4] Strandness et al. "Effect of cilostazol in patients with intermittent claudication: a randomized, double-blind placebo controlled study" Vascular and Endovascular Surgery 2002;36:83-91.

[5] Money et al. "Effect of cilostazol on walking distances in patients with intermittent claudication caused by peripherical vascular disease" J Vasc Surg 1998;27:265-75.

[6] Dawson et al. "A comparison of cilostazol and pentoxifylline for treating intermittent claudication" Am J Med 2000;109:523-30.

[7] Robless et al. "Cilostazol for peripheral disease" Cochrane database of systematic reviews, 24 January 2007.

[8] Hiatt et al. "Long term safety of cilostazol in patients with peripheral artery disease: the CASTLE study (cilostazol : a study in long term effects)" J Vasc Surg 2008;47:330-6.

- unstable coronary disease, coronary intervention during the last 6 months, deep vein thrombosis during the last 3 months, symptomatic cardiac arrhythmia,
- chronic heart failure.

Primary endpoint: maximal walking distance (MWD or absolute claudication distance) measured on treadmill.

Secondary endpoints:
Pain-free walking distance (PWD or initial claudication distance) measured on treadmill.
Quality of life in six trials. The scales used were:
- SF-36, which evaluated quality of life in terms of physical and psychological impact,
- WIQ (walking impairment questionnaire), in terms of impact on walking distances and speeds,
- COM (claudication outcome measures), in terms of walking pain and discomfort (only evaluated in 3 trials).

RESULTS: analysis on an intention-to-treat basis.

Primary endpoint: see table 1
Only the results relating to the dosage validated by the marketing authorization (cilostazol 100 mg twice daily) are presented.

Table 1: Maximal walking distance (MWD)

Trial duration	Treatment	Patients (ITT)	Mean MWD at baseline	Variation in MWD compared with baseline value	Difference vs. placebo	Odds Ratio vs. placebo [95% CI]	p
90-201 12 weeks	CLZ 100 mg Placebo	52 25	141 m 163 m	90 m -17 m	**107 m**	1,41 [1,14 – 1,74]	< 0,01
92-202 24 weeks	CLZ 50 mg CLZ 100 mg Placebo	139 140 140	- 130 m 148 m	- 129 m 27 m	**-** **102 m**	- 1,31 [1,17 – 1,47]	- < 0,01
93-201 12 weeks	CLZ 100 mg Placebo	86 89	262 m 278 m	79 m 35 m	**44 m**	1,13 [1,01 – 1,26]	< 0,05
94-201 24 weeks	CLZ 50 mg CLZ 100 mg Placebo	128 124 125	- 119 m 120 m	- 78 m 20 m	**-** **58 m**	- 1,21 [1,09 – 1,35]	- < 0,01
94-203 16 weeks	CLZ 100 mg Placebo	119 120	211 m 219 m	96 m 31m	**65 m**	1,29 [1,17 – 1,41]	< 0,01
94-301 24 weeks	CLZ 100 mg PEN 400 mg Placebo	123 118 122	128 m 135 m 128 m	86 m 87 m 53 m	**34 m** **-1 m**	1,06 [0,94 – 1,18] 0,99 [0,88 – 1.11]	NS NS
95-201 12 weeks	CLZ 100 mg CLZ 150 mg Placebo	60 53 66	122 m - 123 m	36 m - 37 m	**-1 m** **-**	1,02 [0,88 – 1,18] -	NS -
96-202 24 weeks	CLZ 100 mg PEN 400 mg Placebo	205 212 226	241 m 238 m 234 m	107 m 64 m 65 m	**42 m vs pbo** **43 m vs PEN** **PEN vs pbo : -1m**	1,15 [1,06 – 1,25] 1,16 [1,07 – 1.26] 0,99 [0,92 – 1,07]	< 0,01 < 0,01 NS
PACE 98-213 24 weeks	CLZ 100 mg PEN 400 mg Placebo	218 222 231	138 m 146 m 140 m	60 m 77 m 59 m	**1 m vs pbo** **-17m vs PEN** **PEN vs pbo : 18 m**	1,03 [0,95 – 1,12] 0,98 [0,90 – 1,07] 1,05 [0,97 – 1,14]	NS NS NS

PEN = pentoxifylline / CLZ = cilostazol (PLETAL) / pbo = placebo

The effect size of cilostazol (PLETAL) varied according to the trial: gain of -1 to 107 meters in maximal walking distance compared with the placebo. The heterogeneity of the results observed makes them difficult to explain.

Secondary endpoints:
1/ Pain-free walking distance

Table 2: Pain-free walking distance (PWD)

Trial	Treatment	Patients (ITT)	Mean PWD at baseline	Variation in PWD compared with initial state	Difference vs. placebo	Odds Ratio vs. placebo [95% CI]	p
90-201	CLZ 100 mg Placebo	52 25	70 m 77 m	43 m 4 m	**41 m**	1,35 [1,11 – 1,65]	< 0,01
92-202	CLZ 50 mg CLZ 100 mg Placebo	139 140 140	- 70 m 72 m	- 68 m 23 m	**-** **44 m**	- 1,31 [1,16 – 1,48]	- < 0,01
93-201	CLZ 100 mg Placebo	86 89	142 m 122 m	61 m 56 m	**5 m**	1,08 [0,92 – 1,27]	NS
94-201	CLZ 50 mg CLZ 100 mg Placebo	128 124 125	- 64 m 68m	- 47 m 20 m	**-** **27 m**	- 1,22 [1,08 – 1,38]	- < 0,01
94-203	CLZ 100 mg Placebo	119 120	119 m 130 m	77 m 48 m	**29 m**	1,20 [1,06 – 1,36]	< 0,01
94-301	CLZ 100 mg PEN 400 mg Placebo	123 118 122	78 m 81 m 75 m	52 m *N/A* 37 m	**16m vs pbo** **N/A vs PEN**	1,01 [0,90 – 1,14] 0,98 [0,87 – 1,11]	NS NS
95-201	CLZ 100 mg CLZ 150mg Placebo	60 53 66	66 m - 67 m	38 m - 34 m	**4 m** **-**	1,05 [0,89 – 1,24] -	NS -
96-202	CLZ 100 mg PEN 400 mg Placebo	205 212 226	124 m 126 m 122 m	94 m 74 m 57 m	**37 m vs pbo** **20 m vs PEN** **PEN vs pbo : 18 m**	1,23 [1,12 – 1,36] 1,13 [1,02 – 1,24] 0,99 [0,92 – 1,07]	<0,01 <0,05 NS
PACE 98-213	CLZ 100 mg PEN 400 mg Placebo	231 222 218	75 m 77 m 75 m	47 m 63 m 46 m	**1 m** **-16m vs PEN** **PEN vs pbo : 17 m**	1,02 [0,92 – 1,13] 0,94 [0,85 – 1,05] 1,08 [0,97 – 1,19]	NS NS NS

N/A: not available - PEN = pentoxifylline / CLZ = cilostazol (PLETAL) / pbo = placebo

The effect size of cilostazol (PLETAL) varied according to the trial: gain of 1 to 44 meters in pain-free walking distance compared with the placebo. The heterogeneity of the results observed makes them difficult to explain.

2/ Quality of life
SF 36: an improvement in terms of physical impact, including mobility and pain, was observed in the patients treated with cilostazol (PLETAL) compared with the placebo in three of the six trials. No difference in terms of psychological impact was demonstrated.

WIQ: an improvement in terms of perception of walking speed was observed in the patients treated with cilostazol (PLETAL) compared with the placebo in two of the six trials.

COM: a reduction in walking pain and discomfort was observed in the patients treated with cilostazol (PLETAL) compared with the placebo in only one of the three trials that used this scale.

3.1.2. Pooled analyses of placebo-controlled trials

The data from the placebo-controlled trials presented above were grouped into two reviews:

- the first, comprising eight trials (not including the PACE 98-213 trial), was conducted by the Cochrane group[7],
- the second, comprising nine trials, was conducted by OTSUKA and filed with the marketing authorization.

Cochrane Review
This review assessed the effects of cilostazol (PLETAL) in patients with stable intermittent claudication. The eight trials selected were randomized, double-blind, placebo-controlled trials with or without active comparators.

Treatments: The treatment lasted 12 to 24 weeks:
- cilostazol 50, 100 or 150 mg twice daily
- pentoxifylline 400 mg three times daily,
- placebo

Endpoints:
Primary endpoint: Pain-free walking distance (PWD),
Secondary endpoints: Maximal walking distance (MWD), cardiovascular mortality and number of cardiovascular events.

RESULTS: 2726 patients were randomized and included in the ITT analysis:
Primary endpoint: Pain-free walking distance (PWD)
An improvement in PWD was observed in the patients treated with cilostazol (PLETAL) compared with the placebo: 31.1 m, 95% CI [21.3 – 40.9].

Secondary endpoints:
- *Maximal walking distance (MWD)*
An improvement in MWD was observed in the patients treated with cilostazol (PLETAL) compared with the placebo: 49.7 m, 95% CI [24.2 – 75.2].

- *Morbidity/mortality:*
No difference in terms of cardiovascular mortality or cardiovascular events was observed.

Pooling of the nine trials (filed and analysed by the marketing authorization)
This analysis evaluated the efficacy and safety of cilostazol (PLETAL) in patients with intermittent claudication. It includes the nine trials available. The results do not add any additional information to that contained in the above-mentioned Cochrane Review.

Results: 3143 patients were randomized and included in the ITT analysis:
- CLZ 50 mg twice daily (n = 267),
- CLZ 100 mg twice daily (n = 1116),
- CLZ 150 mg twice daily (n = 73), not included in the meta-analysis
- placebo twice daily (n = 1135),
- pentoxifylline 400 mg three times daily (n = 552)

An improvement in MWD (primary endpoint) was observed in the patients treated with cilostazol (PLETAL) compared with the placebo in six of the nine trials: gain of 39 m, OR = 1.15 [1.11 - 1.19].

An improvement in PWD (secondary endpoint) was also observed: gain of 18 m, OR = 1.16 [1.11 - 1.21].

3.1.3. CASTLE trial
Objective: To evaluate the long-term impact, in terms of mortality, of cilostazol (PLETAL) compared with a placebo in 1435 patients with intermittent claudication.

Method: Randomized, placebo-controlled, parallel-group, double-blind trial in patients within intermittent claudication, followed up 3 years.

Inclusion criteria: Patients over 17 years old with intermittent claudication

Initial primary endpoint : Mortality, all causes.
N.B.: In July 2004, the trial was prematurely stopped after 34 months by agreement with the FDA because the mortality rate was lower than specified in the protocol (based on historical data), and would not allow sufficient power to be achieved or a response to be obtained to the objective defined.

Treatments:
- cilostazol (PLETAL), 100 mg twice daily, n=717,
- placebo, n=718.

RESULTS:
The patients included in the trial had a mean age of 66 years; 30% were smokers, 80% suffered from hypertension, 35% were diabetics, and 80% were hypercholesterolaemics. They received the following combined treatments: aspirin (70%), clopidogrel (27%), warfarin (12%) and statins (70%).

After 36 months' treatment, no difference was observed in terms of mortality: 49 deaths in the cilostazol group (PLETAL) vs. 52 in the placebo group (hazard ratio = 0.94 [0.64 ; 1.39], NS).

3.2. Safety
The safety evaluation of cilostazol 100 mg (PLETAL) twice daily is based on the following data:
- medium-term data resulting from nine placebo-controlled clinical trials (*see table 3*),
- long-term data from the CASTLE trial.

Table 3: Most frequent adverse events (>10%)

Trial	Treatment	Gastro-intestinal disorders*	Headache	Palpitations	Vertigo	Peripheral oedema
90-201	CLZ Placebo	44% 15%	20% 15%	-	-	-
92-202	CLZ Placebo	37% 12%	35% 15%	11% 0%	-	-
93-201	CLZ Placebo	33% 16%.	33% 13%	-	13% 4%.	12% 5%,
94-201	CLZ Placebo	36% 12%.	41% 12%.	-	-	-
94-203	CLZ Placebo	29% 12%.	30% 9%	-	13% 5%.	-
94-301	CLZ PEN Placebo	61% 43% 29%	38% 11% 15%	-	-	-
95-201	CLZ Placebo	28% 9%	39% 10%	-	11% 7%	8% 7%
96-202	CLZ PEN Placebo	34% 13% 6%	28% 11% 12%	17% 2% 1%.	-	-
PACE 98-213	CLZ PEN Placebo	13% 11% 6%	17% 11% 6%	10% 2% 3%	-	-

**diarrhoea, flatulence, nausea and abnormal stools*

CASTLE trial:
A total of 618 adverse events were observed in 329 patients, 203 (28.3%) of whom were treated with cilostazol (PLETAL) vs. 126 (17.5%) with the placebo.

The adverse events most frequently observed were:
- diarrhoea: 78 (10.9%) of patients treated with cilostazol (PLETAL) vs. 48 (6.7%) with the placebo,
- headache: 75 (10.5%) vs. 35 (4.9%),
- palpitations: 38 (5.3%) vs. 18 (2.5%).

The severe adverse events observed were:
- dyspnoea: 7(1%) vs. 3 (0.4%),
- cerebrovascular accident: 7(1%) vs. 15 (2.1%),
- carotid artery stenosis: 5 (0.7%) vs. 11 (1.5%),
- occlusion of femoral artery: 3 (0.4%) vs. 7 (1%),
- cardiac arrest: 2 (0.3%) vs. 7 (1%),
- haemorrhage: 18 (2.5%) vs. 22 (3.1%).

3.3. Conclusion

The efficacy and safety of cilostazol (PLETAL) 100 mg twice daily in patients with stable, moderate intermittent claudication (no pain at rest and no signs of peripheral tissue necrosis) were evaluated in nine placebo-controlled trials after 12, 16 and 24 weeks. A pooled analysis of these trials was also conducted.

The trials presented demonstrated the symptomatic effect of cilostazol (PLETAL) on maximal walking distance MWD (primary endpoint) and pain-free walking distance PWD (secondary endpoint) in tests conducted on a treadmill under standard conditions. However, the extent of the effect of cilostazol (PLETAL) varied according to the trial, with a very limited gain in the patients treated with cilostazol compared with those treated with the placebo, namely:
- -1 to 107 m for maximal walking distance,
- 1 to 44 m for pain-free walking distance.

In the Cochrane Review, an improvement in PWD (primary endpoint) and MWD (secondary endpoint) was observed in the patients treated with cilostazol (PLETAL) compared with the placebo: a gain of 31.1 m, 95% CI [21.3 – 40.9] and 49.7 m, 95% CI [24.2 – 75.2] respectively.

In the CASTLE trial, after 36 months' treatment, no difference in mortality was observed in the patients treated with cilostazol (PLETAL) compared with the placebo.

The adverse events most frequently observed (>10% of patients) were:
Gastrointestinal disorders (diarrhoea, flatulence, nausea and abnormal stools), headache, palpitations, vertigo and peripheral oedema.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Intermittent claudication is a symptom of atheromatous disease which can have serious functional consequences (disability, amputation, loss of independence) and cause a deterioration in the quality of life.

These medicinal products are symptomatic treatments.

The efficacy/safety ratio of these medicinal products is low

Public health benefit:

The public health burden represented by POAD is moderate on the whole, having regard to the deterioration in the quality of life and the cardiovascular and functional consequences for which the serious forms of the disease are mainly responsible; however, the burden represented by intermittent claudication (POAD Stage II) is low.

Reducing the functional limitations associated with chronic disorders and improving the quality of life of the patients suffering from them are established public health priorities (Public Health Act and improved quality of life plan for patients suffering from chronic illnesses).

The available data do not suggest that PLETAL is likely to have an additional impact on reducing morbidity/mortality or improving the quality of life of patients suffering from intermittent claudication, compared with the present treatment.

Consequently, no public health benefit is expected for PLETAL.

There are alternative drugs available.

The actual clinical benefit of these medicinal products is provisionally classed as low pending the results of the reassessment of other reimbursable medicinal products with the same therapeutic aim.

4.2. Improvement in actual benefit

PLETAL does not provide any improvement in actual benefit (IAB V) compared with the other available treatments.

4.3. Therapeutic use[9, 10, 11, 12, 13, 14, 15, 16, 17 18, 19]

Patients with claudication present a high cardiovascular risk.

The treatment of intermittent claudication has two objectives:

- to identify and treat the associated cardiovascular risk factors in order to prevent cardiovascular events,
- to achieve a functional improvement in claudication and the resulting quality of life.

- Management of cardiovascular risk factors:

The treatment of these arteritic patients is based on global treatment which combines:
1/ Treatment of the associated cardiovascular risk factors:
- smoking (giving up smoking),
- excess weight (target BMI<25kg/m^2),
- diabetes (target value HbA1C < 6.5%) ,
- dyslipidaemia,
- essential hypertension.

2/ Prevention of cardiovascular complications:
Patients suffering from POAD are at high cardiovascular risk and require long-term treatment which combines the following three types of therapy:

- a platelet aggregation inhibitor: low-dose aspirin (75-160 mg/day) or clopidogrel (75 mg/day),
- a statin,
- an ACE inhibitor, the dose being gradually increased subject to blood pressure and serum creatinine monitoring, or a beta-blocker.

- Symptomatic treatment

1/ Physical exercise:
As a general rule, the symptomatic treatment of intermittent claudication of arterial origin is primarily based on a supervised walking training programme (grade B). Supervised vascular rehabilitation is an effective treatment for intermittent claudication. It is superior to mere walking advice, and should be offered as first-line therapy (grade B). It is given in a hospital or outpatient clinic, after assessment of coronary tolerance of stress, on the basis of a supervised, customized programme, involving regular assessments by means of walking tests. The programme comprises at least 3 weekly one-hour sessions, and lasts at least 3 months.

2/ Medication
The objective of pharmaceutical treatment of intermittent claudication is to reduce the functional impairment and therefore improve the patient's quality of life, especially by increasing walking distance.

[9] Jackson et al. "antithrombotic therapy in peripheral arterial occlusive disease", Chest, 2001, 119, 283-299.
[10] Burns et al. "Management of peripheral arterial disease in primary care", BMJ, 2002, 326, 584-588.
[11] ACC/AHA, Guidelines for management of patients with peripheral arterial disease", 2006.
[12] The Dutch college of General Practitioners "NHG Practice Guideline: Peripheral arterial disease", December 1999.
[13] Canadian cardiovascular society "Consensus conference: peripheral arterial disease", 2005.
[14] Clagett et al. "Antithrombotic therapy in peripheral arterial occlusive disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy", Chest 2004 Sep;126(3 Suppl):609S-26S
[15] Prise en charge de l'artériopathie chronique athéroscléreuse des membres inférieurs, HAS 2006.
[16] Carpentier et al. "Epidémiologie de l'artériopathie des membres inférieurs d'origine athérothrombotique", Arch. Mal. Cœur et vaisseaux, tome 98, octobre 2005.
[17] Leng GC et al., "Exercise for intermittent claudication", The Cochrane collaboration, April 2000.
[18] "Recommandations de la société française de cardiologie concernant la pratique de la réadaptation cardiovasculaire chez l'adulte" Archives des maladies du cœur et des vaisseaux, tome 95, n°10, octobre 2002.
[19] Hankey et al. "Medical treatment of peripheral disease", JAMA February, 1, 2006 ; 295 : 547-553.

According to the HAS Guidelines, no trial has demonstrated a favourable effect of vasodilators on the systemic complications of the disorder, or on the long-term prevention of arterial deterioration of the limb and amputation risk.

ACC/AHA 2006 and TASC II, 2007 recommend cilostazol (100 mg per os twice daily) to improve the symptoms and increase the walking distance in patients with intermittent claudication (in the absence of heart failure).

4.4. Target population

The target population of cilostazol (PLETAL) corresponds to the population of patients suffering from intermittent claudication with no pain at rest and no signs of peripheral tissue necrosis, namely POAD Stage II.

POAD Stage II is a symptom of atheromatous disease mainly affecting men, and is more frequent in elderly patients. According to the TASC II 2007 consensus conference, the prevalence is 3% in patients aged 40-60 years and 6% in patients aged over 60 years. This prevalence increases with age. Only 5% of patients present intermittent claudication.

Based on the French population [INSEE, 2008], the population suffering from intermittent claudication who would benefit from symptomatic treatment amounts to some 1,300,000 patients.

The reference symptomatic treatment corresponds to the prescription of supervised physical exercise [HAS Recommendations, April 2006]. However, supervised physical exercise is contraindicated in 9-34% (about 20% on average) of these patients (severe coronary disease, musculoskeletal limitations, neurological deficiencies) [TASC II, Norgren and Hiatt, 2007].

On these bases, the target population of cilostazol (PLETAL) can be estimated at approximately 260,000 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for hospital use and various public services in the indications and at the posology in the marketing authorisation.

Packaging: Appropriate for the prescription conditions.

Reimbursement rate: 35%