National PBM Drug Monograph

Cilostazol (Pletal®)

December 2004

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

FDA-approved Indication: Cilostazol is FDA approved for the reduction of symptoms of intermittent claudication, as indicated by increased walking distance. Potential off label use includes restenosis prevention post coronary stent placement.

Dosing: The recommended dose of cilostazol is 100 mg given orally, twice daily. The agent should be taken 30 minutes before or 2 hours after a meal due to changes in bioavailability when taken concomitantly with food. The dose should be decreased to 50 mg twice daily in patients receiving concurrent therapy with CYP3A4 inhibitors (i.e.; erythromycin, ketoconazole). There are no recommendations for dosage alterations in the elderly, mild hepatic impairment or mild to moderate renal impairment

Safety: It is important to consider the cardiac safety of the agent since it is a phosphodiesterase inhibitory agent and is contraindicated in heart failure patients. An analysis of the clinical trials as well as post marketing reports have not shown a difference in all cause mortality from cilostazol in reference to placebo or pentoxifylline. The most commonly reported adverse effects include headache, diarrhea, peripheral edema and palpitations.

Efficacy: Clinical trials of this agent have demonstrated statistically significant improvements in treadmill walking distance as measure by initial and absolute claudication distance. Additionally, quality of life was rated as improved in comparison to placebo. The current available standard to treat claudication, pentoxifylline, has been compared to cilostazol. In this trial cilostazol showed statistically significant improvement in walking distance measures in comparison to pentoxifylline and placebo. Interestingly, this trial showed no improvement for pentoxifylline treated patients over placebo. The recent Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy recommends that cilostazol be use din patients with disabling claudication that have not responded to conservative measures and are not current surgical candidates. The use of cilostazol is not recommended in patients with less-disabling claudication

Conclusion: Cilostazol has benefit over placebo in the treatment of disabling claudication. Validation of the efficacy measures of used in the trials, measurement of walking distance using treadmill testing, to a clinical benefit has not been defined. Additionally, the contribution of placebo response in the trials needs to be defined. In the prevention of restenosis, cilostazol has proven equivalence to ticlopidine with fewer adverse events. Recent trials have demonstrated superiority of cilostazol to aspirin in larger randomized trials addressing restenosis prevention. Anecdotal evidence suggests cilostazol may improve lower extremity wound healing however the evidence is limited by a lack of controlled trials. The safety of the agent has been evaluated in both post marketing reports and via a safety database. The adverse events have been similar in both incidence and type to those seen in the clinical trials of the agent.

Recommendation: It is recommended that cilostazol not be added to the National or VISN formulary and criteria for its use be developed.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating cilostazol for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[1-12]

Cilostazol is a quinolone derivative that displays reversible, selective inhibition of the phosphodiesterase-III isoenzyme. This mediates the primary and secondary platelet aggregation response to adenosine diphosphate, collagen, epinephrine, thrombin and arachidonic acid. The major pathway of inhibition involves suppression of cyclic adenosine monophosphate (cAMP) degeneration resulting in inhibition of platelet aggregation causing subsequent vasodilation. Although cilostazol inhibits platelet aggregation it appears to have no effect on bleeding times.[8,9] Cilostazol has been shown to produce an anti-hyperlipidemic effect in diabetic patients with intermittent claudication (IC).[10] In animal studies it has been shown to inhibit proliferation of vascular smooth muscle cells.

The pharmacokinetics of cilostazol have been well documented in normal volunteers.[11] These results may be extrapolated to patients with peripheral arterial disease (PAD) provided there is no significant impairment of hepatic function. Peak plasma concentrations occurred approximately three hours after oral dosing. The plasma half life of the agent is 11 hours. Cilostazol is highly protein bound and undergoes hepatic metabolism with the major pathway being CYP3A4 and the lesser pathway being CYP2C19. This agent possesses two active metabolites which account for half of its pharmacologic activity. The oral bioavailability of cilostazol can be increased by administration with food.[12] The pharmacokinetic profile of the agent appears unchanged in patients with mild hepatic disease and in mild to moderate renal impairment. Increases in cilostazol plasma concentrations were seen in severe renal failure but this was not associated with an increase in pharmacologic activity.

FDA Approved Indication(s) and Off-label Uses[1]

Cilostazol is FDA approved for the reduction of symptoms of intermittent claudication, as indicated by increased walking distance. Its' off label uses has been in restenosis prevention post coronary stent placement.

Current VA National Formulary Alternatives

Pentoxifylline 400 mg ER TAB (Trental®)

Dosage and Administration[1]

The recommended dose of cilostazol is 100 mg given orally, twice daily. The agent should be taken 30 minutes before or 2 hours after a meal due to changes in bioavailability when concomitantly with food. The dose should be decreased to 50 mg twice daily in patients receiving concurrent therapy with CYP3A4 inhibitors (i.e.; erythromycin, ketoconazole). There are no recommendations for dosage alterations in the elderly, mild hepatic impairment or mild to moderate renal impairment.

Efficacy [13-18]

Efficacy Measures

The Peripheral Artery Questionnaire (PAQ) is a 20-item questionnaire developed to meet this need by quantifying patients' physical limitations, symptoms, social function, treatment satisfaction, and quality of life

ABI. The ABI is a rapid, noninvasive, and reliable measure that detects and quantifies PAD. ABI is defined as the ratio of the ankle systolic blood pressure (SBP) compared with that in the arm. Studies have shown this method to provide an overall assessment of cardiovascular health and identify individuals who are at particularly high risk for morbidity and mortality.[18–21] The sensitivity of the ABI has been reported in clinical trials to be approximately 95%, with a specificity of near 100%.

Exercise Treadmill Test (ETT). To determine walking ability, all study participants performed an ETT using the Skinner-Gardner protocol. The Skinner-Gardner protocol uses a graded workload, with a constant speed of 2 mph and an increase in grade of 2% every 2 minutes. During the ETT, standardized verbal encouragement was given, and all subjects were continuously monitored for hemodynamic response (heart rate, heart rhythm, and blood pressure) to exercise.

Initial Claudication Distance (ICD). ICD was measured as the distance in meters walked on a graded ETT under standardized conditions before the onset of claudication, regardless of whether this was manifested as muscle pain, ache, cramps, numbness, or fatigue. The ICD was calculated using results from two consecutive treadmill tests that were >/=25% variability in absolute claudication distance.

Absolute Claudication Distance (ACD). ACD for this study was determined by the point of termination or maximum distance walked on the ETT due to claudication. The ACD was calculated using results from two consecutive treadmill tests that were >/=25% variability in ACD.

Summary of efficacy findings [19-37]

There have been several randomized, controlled trials of cilostazol versus placebo. In all of these trials, cilostazol demonstrated benefit over placebo in the primary outcomes of ICD and/or ACD as measured on a treadmill. Please refer to **Table 1** for specifics of these trials. These trials were of a relatively short duration and had high withdrawal rates after randomization. All the trials demonstrated higher withdrawal rates with cilostazol than those seen with placebo.

A single head to head trial has compared the two commonly used agents for claudication. Dawson et al.[20] investigated the effects of cilostazol, pentoxifylline and placebo on the primary outcome measures of ICD and ACD in patients with stable IC. This trial included 698 patients and produced a large placebo effect as well as statistically significant improvements in ICD and ACD in patients receiving cilostazol [percent change 98.3 and 53.9, cilostazol versus placebo, respectively ($p<0.05$)] but not in those receiving pentoxifylline. These findings are in agreement with previous trials of pentoxifylline where only modest improvements were seen.

The manufacturer has proved a sub group analysis from the clinical trials for patients enrolled in VA facilities (N=264) versus non-VA facilities (N=1460). The populations displayed similar demographics however the proportion of men and non-Caucasians was higher in the VA group. Additionally, the VA group had a higher rate of diabetes mellitus, previous MI and longer duration of PAD. The percent mean change from baseline in walking distance for the VA group was 44.5% and the non VA group 58%, both statistically significant from placebo ($p<0.01$). [Internal communication, Otsuka Pharmaceutical, October 2004].

The use of cilostazol has been investigated for the off label indications of coronary stenting and restenosis prophylaxis. The five studies which investigated this use have found conflicting results. This may be

reflected in the size of the trial; early, small trials found a benefit but the more recent larger trials have not demonstrated equivalent findings. The results of these trials are summarized in **Table 2**. There is an ongoing trial (CREST- The Cilostazol for Restenosis Trial) underway.[31] The effects of aspirin plus clopidogrel versus aspirin, clopidogrel and cilostazol are being investigated in 705 patients. Additional trials have shown no differences between cilostazol (and aspirin) and ticlopidine (plus aspirin) with regard to effectiveness and safety for a one-month period when used as an adjunctive therapy after coronary stenting. Ticlopidine may be associated with more side effects. Although cilostazol failed to show a significant reduction in restenosis after PTCA in several of the trials the lesion non-progression rate, which was defined as the incidence of lesions with either no change or regression of coronary stenosis at the PTCA site, was significantly greater with cilostazol.

The use of cilostazol is under investigation for the treatment of chronic lower extremity wounds.[46-48] There are anecdotal case reports which demonstrated an improvement in healing after cilostazol therapy was initiated. In a case series of five patients with severe peripheral artery disease and non-healing lower extremity ischemic ulcerations, complete wound healing was seen in 7-24 weeks after cilostazol initiation.[46] These preliminary findings need to be validated by larger, randomized controlled trials.

In addition to the effects on walking distance, restenosis and quality of life, cilostazol has demonstrated a beneficial effect on plasma lipids. In a meta-analysis of eight randomized, placebo controlled trials including 2,702 patients cilostazol decreased plasma triglycerides 15.85 and increased HDL cholesterol by 12.8%. [36,37]

Adverse Events (Safety Data)[1,38]

A review of the adverse events reported during the clinical trials of cilostazol in addition to post marketing experience was presented by Pratt in 2001.This review includes 1,441 cilostazol treated patients, 973 placebo treated and 355 treated with pentoxifylline. Additionally, post market experience includes 70,430 patient years of cilostazol exposure.

Deaths and Other Serious Adverse Events

An analysis of 1,441 patients who received cilostazol through the clinical trials as well as from four placebo controlled trials conducted in Europe was analyzed for cardiovascular morbidity and mortality. There were 12 deaths (0.8%) in this patient population in comparison to 0.7% in the placebo treated patients (7/973) and 0.6% in those treated with pentoxifylline (2/355). The all cause mortality was not significantly different between these treatment groups.

Common Adverse Events

The most commonly reported adverse effects reported during the clinical trials were headaches, diarrhea, abnormal stools, peripheral edema and palpitations. These effects did not appear to be dependent on the dose of cilostazol utilized in the trial.

Other Adverse Events

Additional adverse events reported in the trials, in declining frequency, include pain, dizziness, pharyngitis, rhinitis, nausea, dyspepsia, tachycardia, asthenia, increased cough, flu syndrome and dyspnea.

Tolerability

Reports of headache were the most common reason for withdrawal from the cilostazol arms of the clinical trials with 1.3% of patients receiving cilostazol 50 mg and 3.7% of those on 100mg withdrawing in comparison to 0.3% of placebo treated patients.

Precautions/Contraindications[1]

Contraindications

Cilostazol is contraindicated in patients with congestive heart failure (CHF) of any severity. Cilostazol and several of its metabolites are inhibitors of phosphodiesterase III. Several drugs with this pharmacological effect have caused decreased survival compared with placebo in patients with class III-IV CHF. In patients without CHF, the long-term effects of PDE III inhibitors (including PLETAL) on survival are unknown.

Drug Interactions[39-44]

Drug-Drug Interactions

Due to the enzymatic pathways involved with cilostazol metabolism the potential for drug interactions exists. Additionally, cilostazol is highly protein bound which may contribute to its interaction potential. Co administration with diltiazem, erythromycin and omeprazole significantly increased cilostazol concentrations by 53%, 47% and 69%, respectively. Strong inhibitors of the CYP3A4 enzyme system would be expected to increase cilostazol concentrations as well. It is recommended that the dosage of cilostazol is halved in patients who are taking drugs known to inhibit CYP3A4 or CYP2C19.

No clinically significant drug interactions have been reported between cilostazol and aspirin or warfarin. However, there is no information on concurrent use of cilostazol and clopidogrel.

Data Compilation Tables

The two meta analysis of the cilostazol trials have focused on percent mean change in walking distance from baseline. Since the trials involved different treadmill protocols, duration of therapy and measures this efficacy measurement has been chosen. This measure has not been correlated to a discrete clinical benefit.

(OUTCOME ON DRUG)	50%
(OUTCOME ON PBO)	27.8%
Treatment duration	12-24 weeks
Relative Risk	79%
Absolute Risk	22%
NNT	4.5

Acquisition Costs

Drug	Dose	Cost/Day/patient ($)	Cost/Year/patient ($)
Cilostazol Pletal®	100 mg twice daily	2.00	730
Cilostazol generic*	100 mg twice daily	2.46	897.90
Pentoxifylline Trental®	400 mg three times daily	1.50	547.50
Pentoxifylline generic	400 mg three times daily	0.24	87.60

* price used is AWP since FSS pricing is not yet available

Pharmacoeconomic Analysis

To date there have been no formal economic analysis conducted for cilostazol. Although the clinical trials of the agent have demonstrated statistically significant improvement in treadmill walking distances, the economic impact of this finding is unknown. .

Conclusions

Cilostazol has benefit over placebo in the treatment of disabling claudication. Validation of the efficacy measures of used in the trials, measurement of walking distance using treadmill testing, to a clinical benefit has not been defined. Additionally, the contribution of placebo response in the trials needs to be defined. In the prevention of restenosis, cilostazol has proven equivalent to ticlopidine with fewer adverse events. Recent trials have demonstrated superiority of cilostazol to aspirin in larger randomized trials. Anecdotal evidence suggests cilostazol may improve lower extremity wound healing however the evidence is limited by a lack of controlled trials. The safety of the agent has been evaluated in both post marketing reports and via a safety database. The adverse events have been similar in both incidence and type to those seen in the clinical trials of the agent. The recent Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy[45] recommends that cilostazol be used in patients with disabling claudication that have not responded to conservative measures and are not surgical candidates. The use of cilostazol is not recommended in patients with less-disabling claudication. This conference recommends either clopidogrel or ticlopidine over cilostazol for patients after stent placement.

Recommendations

It is recommended that cilostazol not be added to the National or VISN formulary and that criteria for its use be developed.

Table 1

Randomized, Placebo Controlled Trials of Cilostazol

Author	Duration (weeks)	N	Functional Status measure	ABI	ACD(m) Cilostazol vs. placebo	ICD(m) Cilostazol vs. placebo	NNT
Dawson, 2000[20]	24	466			350 vs. 300 (p<0.001)	218 vs. 180 (p=0.02)	2
Money, 1998[21]	16	298	Statistical improvement on SF-36 and WIQ	NS for placebo, 0.64 vs. 0.70 (p=0.0125) for C	333 vs. 281 NS	NA	2
Beebe, 1999[22]	24	516	Statistical improvement on SF-36, COM and WIQ	NA	259 vs. 175 (p<0.001)	138 vs. 96 (p<0.001)	1
Dawson, 1998[23]	12	81	NA	NA	113 vs. 85 (p=0.007)	232 vs. 152 (p=0.002)	4
Strandness, 2002[24]	24	394			196 vs. 141 (p=0.0003)	NA	2
Elam, 1998[25]	12	189	NA	NS for placebo 0.66 vs0.73 (p<0.001) for C	335 vs. 304 (p,0.004)	NA	3

Table 2

Trials of Cilostazol for Restenosis

Author	Design	N	Stent use	comparator	Duration of therapy	Restenosis rate	
						comparator	cilostazol
Kamishirado, 2002[26]	RCT	130	Yes	Ticlopidine	6 month	31	13*
Tanabe, 2001[27]	Registry	109	No	Aspirin 81 mg	4 month	43.8	12.5*
Park, 2000[28]	RCT	409	Yes	Ticlopidine	6 month	27	23
Tsuchikane, 1999[29]	RCT	211	No	Aspirin 250 mg	3 month	40	18
Kunishima, 1997[30]	RCT	70	Yes	Aspirin 250 mg	NR	26.8	8.6*

* $p < 0.05$

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