Annex II

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisations

Scientific conclusions

Overall summary of the scientific evaluation of cilostazol containing medicinal products (see Annex I)

Cilostazol is a dihydro-quinolinone derivative that belongs to the pharmacotherapeutic group antithrombotic agents, platelet aggregation inhibitor excluding heparin. Cilostazol is a dihydro-quinolinone derivative that inhibits cyclic adenosine monophosphate (cAMP) phosphodiesterase, suppressing cAMP degradation and thereby increasing cAMP levels in platelets and blood vessels. This leads to inhibition of platelet activation and aggregation and prevents the release of prothrombotic inflammatory and vasoactive substances. The vasodilatory effects of cilostazol may also be mediated through an increase in cAMP. It also inhibits the vascular smooth muscle cell proliferation as well as decreases triglycerides and increases HDL-cholesterol.

The therapeutic indication that has been approved for cilostazol products in Europe is the improvement of the maximal and pain-free walking distances in patients with intermittent claudication (IC), who do not have rest pain and who do not have evidence of peripheral tissue necrosis (peripheral arterial disease (PAD) Fontaine stage II).

This Article 31 referral was initiated by Spain following review of safety reports received in association with cilostazol during the first 18 months of marketing in Spain (cilostazol was licenced in Spain in 2008). The Spanish authority's main concerns centred on reports received of cardiovascular reactions (including fatal cases of MI, angina pectoris and arrhythmias) and haemorrhagic reactions as well as drug interactions. A drug utilisation study conducted in one region of Spain found that patients receiving cilostazol were older and used more concomitant medications than those in the clinical trials. Spain therefore referred cilostazol to the CHMP/EMA, requesting that it gives its opinion under Article 31 of Directive 2001/83/EC, on whether the marketing authorisations for medicinal products containing cilostazol should be maintained, varied, suspended or withdrawn.

Clinical Efficacy

The efficacy of cilostazol has been evaluated in 14 clinical trials which enrolled more than 4000 intermittent claudication (IC) patients. These included eight double-blind controlled phase III trials, two of which compared the efficacy of cilostazol with an active comparator (pentoxifylline) and placebo over 24 weeks. In addition, a phase IV double-blind placebo-controlled efficacy study (PACE study), was performed also with pentoxifylline as active comparator. In total 3,122 patients were randomised and received at least one dose of investigational product in the 9 efficacy trials. The primary endpoint in the nine efficacy trials (called mid-term trials) was maximum walking distance (absolute claudication distance – ACD), measured by exercise treadmill testing. Secondary efficacy endpoints included pain-free walking distance (initial claudication distance – ICD) measured by treadmill exercise; and Quality of Life assessments.

The primary analysis, pre-specified in the protocols, demonstrated a statistically significant longer walking distance in patients receiving cilostazol 100mg bid over placebo. Point estimates in all nine trials favoured cilostazol 100mg bid over placebo and the analysis demonstrated statistical superiority of cilostazol over placebo in six of the nine trials.

A pooled meta-analysis of these trials using the ratio of geometric means for LOG (ACD at last visit/ACD at baseline) for cilostazol vs. placebo demonstrated a treatment effect of 1.15 (95% CI: 1.11 – 1.19) for ACD.

In all efficacy trials cilostazol showed a higher percentage improvement in ACD when compared with placebo and this was statistically significant in 6 of the 9 trials. The range of improvement was between +28% to +100% for cilostazol, and -10% to +42% for placebo in the individual trials. The

increase in walking distance over baseline walking distance with cilostazol treatment was 35% higher than with placebo. Results for secondary efficacy endpoints were consistent with the results for ACD.

Cilostazol's effect on absolute walking distances on the treadmill, expressed as an absolute increase over baseline walking distance ranged from +23m to +109m, compared with -2m to +65m for placebo. The meta-analysis of weighted mean difference (WMD) across the nine trials also demonstrated consistent efficacy of cilostazol across the trials. The WMD estimates a mean improvement from baseline for walking distance of 87.4m for cilostazol 100mg bid and 43.7m for placebo ($p<0.0001$) with a mean baseline walking distance of about 133m (66% improvement with cilostazol). It was noted by the CHMP that the increase in walking distance on flat ground is likely to be greater than the increase measured on the treadmill – which is set on an incline.

Data relating to quality of life assessments and responder analyses was considered in the assessment as these data give some insight into the issue of the clinical relevance of the treatment effect, which is complicated by the fact that patients are likely to have different levels of benefit depending on the severity of their intermittent claudication (IC) symptoms. Pooled meta-analyses of patient reported outcomes from the short-form health survey (SF-36) and the Walking Impairment Questionnaire (WIQ) demonstrated significant effects of cilostazol over placebo on physical functioning and the physical component score of the SF-36, as well as significant improvements in WIQ speed and distance scores. A greater proportion of 'completers' treated with cilostazol were classified as 'responders' than those treated with placebo (39.6%, vs. 26.3%) with 'responders' defined as those patients whose walking distance had improved by 50% or more from baseline.

The CHMP was therefore of the opinion that cilostazol has a statistically significant, albeit modest effect on walking distances in patients with IC and that some patients may benefit to a clinically relevant degree.

Clinical safety

Safety data for cilostazol available from the efficacy trials (mid-term trials), the long-term safety trial CASTLE and stroke prevention studies, as well as case reports from spontaneous sources and non-interventional studies were considered in this review.

No major safety concerns were identified from the clinical trials. The most common adverse events included headache, diarrhoea, abnormal stools, dizziness, palpitations and tachycardia, already listed in the Product Information. No signal for increased mortality was observed in clinical trials, including the CASTLE study.

The primary objective of the CASTLE trial was to assess the long-term effect of cilostazol on all-cause mortality. The CASTLE study included patients who were treated up to 3 years. The study was terminated prematurely as a result of a lower than expected event rate and higher than expected drop-out rate. The hazard ratio for mortality (cilostazol vs. placebo) was 0.94, 95% CI [0.63-1.39].

The results from clinical trials did not generate any signal of serious cardiac arrhythmic events, but a small number of serious events (ventricular tachycardia, electrocardiogram QT prolongation (including Torsade de Pointes)) were received from spontaneous sources/non-interventional studies and some of these were considered compatible with the chronotropic effects of cilostazol. The CHMP considered that causality was difficult to assess in these reports, especially given the level of confounding due to the background conditions in these patients. However, it was noted that the activity of cilostazol as a phosphodiesterase enzyme (PDE-3) inhibitor raises a potential safety concern over cardiac arrhythmias that may result from the increase in resting heart rate (cilostazol has been demonstrated to increase heart rate by ~5.1 and ~7.4 beats per minute at the authorised doses). Palpitations and tachycardia were well-documented in clinical trials. In view of this, the CHMP considered that cilostazol should be

contraindicated in patients with a history of severe tachyarrhythmia and that additional warnings should be introduced in the PI.

Other adverse events of interest such as myocardial ischemia (myocardial infarction, angina pectoris, coronary artery disease), congestive heart failure and hypotension, were also identified during the mid-term efficacy clinical trials, with a higher incidence in the cilostazol group compared to placebo. However these imbalances involved small numbers of events. It was noted that there was a small excess of cases of heart failure (cilostazol: 2.9%, vs. placebo: 2.4%) and hypotension (cilostazol: 0.7%, vs. placebo: 0.1%) in the CASTLE study. The CHMP therefore considered that cilostazol should be contraindicated in patients with unstable angina pectoris, myocardial infarction within the last 6 months, or a coronary intervention in the last 6 months, and that additional warning should be included in the PI.

The anti-platelet activity of cilostazol also raised a concern for haemorrhagic events. In the CASTLE trial, a lower bleeding event rate was observed in the cilostazol arm than in the placebo arm and the use of concomitant aspirin did not increase the frequency of bleeding in the sub-group treated with cilostazol. However, concomitant aspirin and clopidogrel treatment together increased the risk of bleeding in the cilostazol group compared with the placebo patients. In view of this, the CHMP considered that patients treated concomitantly with two or more additional antiplatelet or anticoagulant agents (e.g. aspirin acetylsalicylic acid, clopidogrel, heparin, warfarin, acenocoumarol, dabigatran, rivaroxaban or apixaban) should not be treated with cilostazol-containing products.

Cilostazol is mainly metabolised by CYP3A4, and CYP2C19 and has two main active metabolites, OPC-13015 (dehydrocilostazol, 3-7 times more potent than cilostazol), and OPC-13213 (trans-hydroxy-cilostazol, 2 – 5 times less potent than cilostazol). Given the increase in exposure to cilostazol resulting from concomitant use of CYP3A4 and CYP2C19 inhibitors (such as erythromycin, ketoconazole and omeprazole), the CHMP considered that there is a high potential for interactions with other medicinal products that could increase the risks associated with cilostazol and therefore considered that the SmPC wording in section 4.5 should be strengthened. The CHMP also recommended a dose reduction to 50mg bid of cilostazol during concomitant use with such medicines. This reduced dose has been shown to be clinically effective in clinical trials in patients using CYP3A4 or CYP2C19 inhibitors.

Overall conclusion

Cilostazol is associated with a modest but statistically significant increase in walking distance compared with placebo in patients with IC, and this has also been demonstrated using quality of life measurements. In terms of safety, clinical trial data showed that the most commonly-reported adverse events are headaches, diarrhoea, dizziness, palpitations, peripheral oedema and tachycardia, and these adverse events were listed in the product information. However, the pharmacological effects of cilostazol suggest that it may cause more serious cardiac arrhythmias in some patients. In addition, considering its anti-platelet activity, cilostazol is expected to increase the risk of bleeding. However, causality and magnitude of this risk is difficult to quantify given the lack of a clear signal in clinical trials and given the level of confounding due to the background concomitant medication used by these patients. The concerns relating to interactions with other medications (in particular CYP3A4 and CYP2C19 inhibitors) and the possibility of an increased risk for adverse effects have been addressed by the recommendation of a dose reduction to 50mg bid in patients taking concomitant medicines that inhibit these enzymes.

In view of the modest benefits of cilostazol and of the existing safety concerns, the Committee is of the view that the use of cilostazol should be restricted to those who would benefit the most from treatment, i.e. patients for whom life-style modifications (stopping smoking and exercise programs)

and other appropriate interventions have not provided sufficient benefit. Suitability of treatment with cilostazol should be carefully considered, alongside other treatment options such revascularisation.

At the request of the CHMP, an ad-hoc expert advisory group meeting was convened in February 2013. The experts were first asked to discuss the current standard approach to the clinical management of peripheral arterial occlusive disease (PAOD), the characteristics of the patients treated with cilostazol and the clinical relevance of the benefits of cilostazol. The experts were of the view that cilostazol has a beneficial effect in patients with limiting intermittent claudication who cannot manage an exercise program in getting such patients over "the first hurdle" that would then allow them to continue progression of their walking distance through exercise. It was recognised by the experts that the benefit of cilostazol products was small but was clinically significant, and enough to restore independence for some patients and to get them started with their rehabilitation program. The need to review the patient's response to treatment at 3 months and to continue treatment only if positive was agreed by all. The experts acknowledged that minor adverse events were commonly seen in some patients but no major side effects were recorded by any of the experts. The expert group noted the spontaneous reports of haemorrhage when used with one or two antiplatelet drugs, but were reassured by the absence of evidence from the published placebo-controlled studies. However, they recognised that there is a risk of bleeding with triple therapy and that triple therapy should be avoided (cilostazol and two antiplatelet drugs). The experts agreed that the CASTLE study had some limitations (including early termination and high rate of dropout, study restrictive in certain patient groups, exclusion of high risk patients, and review of the patients by their doctors in a 6-month period) but that some of those were expected with such a long term Phase IV study. It was recognised that less adverse events than expected had been reported. The experts considered that the included patients were a reasonable representation of real-life and it was hard to argue that the study was not reassuring and agreed that cilostazol has shown a consistent trend for being as safe as placebo across the major cardiovascular endpoints. Although a post-hoc analysis, the demonstration that the current accepted CV MACE in studies of new drugs (CV death, non-fatal MI and stroke) was statistically significantly lower in the treatment group was felt to give strong reassurance on CV safety. The group considered that it was feasible to exclude high cardiovascular risk patients in practice, and that this would also limit the risk of drug interaction with antiplatelet agents (as most patients in these groups would receive dual antiplatelet therapy). The proposal from the MAHs to recommend a reduction to 50mg bid in some patient sub-groups was welcomed by the group. Overall, the group was of the view that for a small group of patients with low risk of cardiovascular co-morbidities, limiting intermittent claudication who cannot manage initial exercise rehabilitation, or who are unsuitable for revascularisation, this drug may have a role.

Considering all available data on the safety and efficacy of cilostazol as well as the conclusions of the ad-hoc expert group meeting, the CHMP has agreed on a number of measures including the restriction of the indication to "second-line use, in patients in whom lifestyle modifications (including stopping smoking and [supervised] exercise programs) and other appropriate interventions have failed to sufficiently improve their intermittent claudication symptoms", and the introduction of three new contraindications, in patients with history of severe tachyarrhythmia, patients treated concomitantly with two or more additional anti-platelet/anticoagulant agents and patients with unstable angina pectoris, myocardial infarction within the last 6 months, or a coronary intervention in the last 6 months.

A closer monitoring of treatment success after 3 months instead of 6 months, with a view to discontinuing cilostazol where the treatment effect is considered to be inadequate is now recommended. Also, cilostazol should only be initiated by physicians experienced in the management of intermittent claudication after suitability of treatment with cilostazol has been carefully considered, alongside other treatment options such a revascularisation.

In order to minimise the risk of drug metabolism interaction, warnings have been introduced in the SmPC and it is now recommended to reduce the dose to 50mg bid in patients taking medicines that inhibit CYP3A4 or 2C19.

The pharmacovigilance measures should be increased by submitting 6-monthly PSURs including safety reports focused on cardiovascular adverse events, haemorrhagic adverse events and off-label use.

To ensure that health care professionals are informed of the correct indication for use of the product, the MAH has introduced the following measures: proactive communication to physicians on the Otsuka Europe website, re-training of the Medical Information teams and Sales Force teams in the countries where cilostazol is marketed. The CHMP endorsed a communication i.e. Direct Healthcare Professional Communication (DHPC), to rapidly communicate the outcome of the present review.

In order to measure the effectiveness of the above measures, the CHMP has agreed on two drug utilisation studies (DUS). The first DUS' will obtain baseline data with the objective to describe the characteristics of new users of cilostazol and the duration of the use of cilostazol and discontinuation patterns. The study will also aim to quantify off-label use, describe dosage patterns and identify the medical specialties of physicians prescribing cilostazol. The second DUS will have the objective to evaluate the effectiveness of the proposed SmPC changes, educational initiatives and other implemented risk minimisation measures in terms of the mitigation of off-label use and adherence of prescribers to the SmPC, in comparison with baseline data. The protocol of the studies was agreed by the CHMP.

In addition, the MAH agreed to perform a mechanistic study to provide further insight into the effects on platelet aggregation of cilostazol with aspirin or clopidogrel and their consequences on bleeding time. Excesses in bleeding time during cilostazol treatment outside a prespecified range as to be defined in the protocol will be assessed and appropriate risk minimisation measures will be proposed when the final study report is available.

Benefit –risk balance

The Committee concluded that the benefit-risk balance of cilostazol products for the improvement of the maximal walking distance and maximal pain-free walking distances in patients with intermittent claudication (IC), who do not have rest pain and who do not have evidence of peripheral tissue necrosis (peripheral arterial disease Fontaine stage II) remains positive under normal conditions of use, subject to restrictions, warning, changes to the product information and risk minimisation measures agreed.

Grounds for the variation to the terms of the marketing authorisation

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC on cilostazol-containing medicinal products;
- The Committee reviewed all the data provided by the MAHs in writing and in the oral explanation and the outcome of the ad-hoc expert advisory group meeting;
- The Committee has reviewed all adverse drug reaction data and clinical trial data associated with Cilostazol; in particular the cardiovascular events and bleeding reactions. Although clinical trial data did not substantiate safety concerns raised from spontaneous ADR reporting, the CHMP concluded that the risk of bleeding and some cardiovascular events including tachyarrhythmias cannot be excluded in at-risk patients. The CHMP also concluded that the risk of bleeding was higher in patients treated concomitantly with two or more additional antiplatelet or anticoagulants

agents. The Committee is of the opinion, considering the metabolism of cilostazol, that there is a potential for interactions that could increase the risks associated with cilostazol.

- In view of the above safety concerns, the Committee agreed on a number of risk minimisation measures, including changes to the product information to strengthen the wording of the PI to reduce the risk of haemorrhagic events, cardiac events and potential drug-drug interactions (contra-indication in at-risk patients, recommendation of adjustment of the dose, strengthening of the warning to ensure suitability of the treatment with cilostazol). The CHMP also agreed to the introduction of measures to ensure health care professionals are informed on the conditions of use of the product. Finally The Committee agreed to drug utilisation studies to describe the characteristics of new users of cilostazol and the duration of the use of cilostazol and discontinuation patterns, and thereby to evaluate the effectiveness of the implemented risk minimisation measures;
- The Committee considers that the benefit of cilostazol is modest but that a statistically significant increase in walking distance compared with placebo has been shown in patients with intermittent claudication;
- The Committee is of the opinion that some patients may benefit from cilostazol treatment to a clinically relevant degree; however, in view of the existing safety concerns, the Committee considered it appropriate to restrict use to those who have not responded to lifestyle treatment and to recommend that treatment is only continued in those who have shown a meaningful response within the first 3 months;
- The Committee, as a consequence, concluded that the benefit-risk balance of cilostazol-containing medicinal products is positive under normal conditions of use only for second-line use, in patients in whom lifestyle modifications and other appropriate interventions have failed to sufficiently improve their intermittent claudication symptoms, and subject to the agreed risk minimisation measures, including changes to the product information.

Therefore the CHMP recommended the variation to the terms of the Marketing Authorisations for the cilostazol-containing medicinal products referred to in Annex I, in accordance to the amendments to the Summary of Product Characteristics, Labelling and Package Leaflet set out in Annex III and subject to the conditions set out in Annex IV.