Public Assessment Report

UKPAR

Cilostazol 50 and 100 mg Tablets
(cilostazol)

UK Licence No: PL 04569/1426-1427

Generics [UK] Ltd t/a Mylan
LAY SUMMARY
Cilostazol 50 and 100 mg Tablets
(cilostazol)

This is a summary of the Public Assessment Report (PAR) for Cilostazol 50 and 100 mg Tablets (PL 04569/1426-1427). It explains how Cilostazol 50 and 100 mg Tablets were assessed and their authorisations recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Cilostazol 50 and 100 mg Tablets.

For practical information about using Cilostazol 50 and 100 mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Cilostazol 50 and 100 mg Tablets and what are they used for?
Cilostazol 50 and 100 mg Tablets are ‘generic medicines’. This means that Cilostazol 50 and 100 mg Tablets are similar to ‘reference medicines’ already authorised in the UK called Pletal 50 and 100 mg Tablets (Otsuka Pharmaceuticals Limited; PL 11515/0002-0003).

Cilostazol 50 and 100 mg Tablets are used to treat “intermittent claudication”, which is a cramp-like pain in the legs when walking, caused by insufficient blood supply in the legs. Cilostazol 50 and 100 mg Tablets improve blood circulation in the legs, meaning that patients can walk longer distances without pain.

Cilostazol is only recommended for patients whose symptoms have not improved sufficiently after making lifestyle changes (such as stopping smoking and increasing exercise) and after other appropriate interventions. Patients should maintain these lifestyle changes whilst taking cilostazol.

How do Cilostazol 50 and 100 mg Tablets work?
Cilostazol 50 and 100 mg Tablets belong to a group of medicines called the phosphodiesterase Type 3 inhibitors. They have several actions which include widening of some blood vessels and reducing the clotting activity (clumping) of some blood cells called platelets inside the blood vessels.

How are Cilostazol 50 and 100 mg Tablets used?
Cilostazol 50 and 100 mg Tablets are taken by mouth. The recommended dose is two 50 mg tablets or one 100 mg tablets twice a day (morning and evening). A lower dose may be prescribed for patients taking other medicines which may have an effect on Cilostazol 50 and 100 mg Tablets.

Cilostazol 50 and 100 mg Tablets should be taken with a drink of water 30 minutes before breakfast and the evening meal.

These medicinal products can only be obtained on prescription from a doctor.

For further information on how Cilostazol 50 and 100 mg Tablets are used, refer to the Summaries of Product Characteristics or package leaflet available on the MHRA website.

What benefits of Cilostazol 50 and 100 mg Tablets have been shown in studies?
As Cilostazol 50 and 100 mg Tablets are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicines, Pletal 50 and 100 mg Tablets (Otsuka Pharmaceuticals Limited). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.
What are the possible side effects of Cilostazol 50 and 100 mg Tablets?
Because Cilostazol 50 and 100 mg Tablets are generic medicines and are bioequivalent to Pletal 50 and 100 mg Tablets (Otsuka Pharmaceuticals Limited), their benefits and possible side effects are taken as being the same as those of the reference medicines.

For the full list of all side effects reported with Cilostazol 50 and 100 mg Tablets, see section 4 of the package leaflet available on the MHRA website.

Why was Cilostazol 50 and 100 mg Tablets approved?
It was concluded that, in accordance with EU requirements, Cilostazol 50 and 100 mg Tablets have been shown to have comparable quality and to be bioequivalent to Pletal 50 and 100 mg Tablets (Otsuka Pharmaceuticals Limited). Therefore, the MHRA decided that, as for Pletal 50 and 100 mg Tablets (Otsuka Pharmaceuticals Limited), the benefits of Cilostazol 50 and 100 mg Tablets are greater than their risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Cilostazol 50 and 100 mg Tablets?
A risk management plan has been developed to ensure that Cilostazol 50 and 100 mg Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet for Cilostazol 50 and 100 mg Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about Cilostazol 50 and 100 mg Tablets
Marketing Authorisations were granted in the UK on 23rd February 2015.

The full PAR for Cilostazol 50 and 100 mg Tablets follows this summary.

For more information about treatment with Cilostazol 50 and 100 mg Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in April 2015.
TABLE OF CONTENTS

I  Introduction  Page 5
II  Quality aspects  Page 6
III  Non-clinical aspects  Page 7
IV  Clinical aspects  Page 8
V  User consultation  Page 12
VI  Overall conclusion, benefit/risk assessment and recommendation  Page 12

Table of content of the PAR update  Page 16
I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Generics [UK] Ltd t/a Mylan Marketing Authorisations for the medicinal products Cilostazol 50 and 100 mg Tablets (PL 04569/1426-1427). The products are prescription-only medicine (POM) indicated for the improvement of the 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 (peripheral arterial disease Fontaine stage II).

Cilostazol is for 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.

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended. The applicant has cross-referred to Pletal 50 and 100 mg Tablets, which were originally authorised to Otsuka Pharmaceuticals Limited (PL 11515/0002-0003) on 21st March 2000.

Cilostazol and several of its metabolites are phosphodiesterase III inhibitors which suppress cyclic AMP degradation, resulting in increased cAMP in a variety of tissues including platelets and blood vessels.

Two bioequivalence studies were submitted to support these applications comparing the applicant’s test products Cilostazol 50 and 100 mg Tablets (Adamed Sp. z o.o.) with the reference products Pletal 50 and 100 mg Tablets (Otsuka Pharmaceutical Europe Ltd) under fasting conditions. The applicant has stated that the bioequivalence studies were conducted in compliance with Good Clinical Practises (GCP) requirements.

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that these applications were based on products being generic medicinal products of originator products that have been in clinical use for over 10 years.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Cilostazol 50 and 100 mg Tablets outweigh the risks and Marketing Authorisations were granted.
II QUALITY ASPECTS

II.1 Introduction
Each tablet contains 50 and 100 mg of cilostazol, as active ingredient. The excipients present are maize starch, cellulose, microcrystalline, carmellose calcium, hypromellose and magnesium stearate. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for these excipients.

None of the excipients contain materials of animal or human origin. Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

The finished products are packed into polyvinyl chloride (PVC)/polyvinlidene chloride (PVdC)-aluminium blisters containing 7, 10, 14 and 56 tablets per carton. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2. Drug Substance
INN: Cilostazol
Structural formula:

![Structural formula](image)

Molecular formula: \( C_{20}H_{27}N_{5}O_{2} \)
Molecular mass: 369.46 g/mol
Appearance: White to off-white crystal.
Solubility: Cilostazol is freely soluble in chloroform, DMSO, slightly soluble in methanol, ethanol and in acetone, practically insoluble in water and in ether.

Cilostazol is the subject of an active substance master file (ASMF).

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analyses data are provided that comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.
Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, tablets containing 50 mg and 100 mg cilostazol per tablet that are bioequivalent to the reference products Pletal 50 and 100 mg Tablets (Otsuka Pharmaceuticals Limited). A satisfactory account of the pharmaceutical development has been provided.

Comparative impurity and in-vitro dissolution profiles have been provided for the proposed and originator products.

Manufacture of the products
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing processes. The manufacturing process has been validated and has shown satisfactory results. Process validation data on pilot scale batches have been provided. Since there is small difference between the size of the pilot batch and commercial scale batch, process validation on consecutive commercial scale batches is not necessary to be performed.

Finished Product Specifications
The finished product specifications proposed are acceptable. The test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Products
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years with no special storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of these applications from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS
III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of cilostazol are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for these product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Cilostazol 50 and 100 mg Tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

There are no objections to the approval of these applications from a non-clinical viewpoint.

IV CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology of cilostazol is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamic or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for these type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of cilostazol.

Based on the data provided, Cilostazol 50 and 100 mg Tablets can be considered bioequivalent to Pletal 50 and 100 mg Tablets (Otsuka Pharmaceutical Europe Ltd.).

IV.2 Pharmacokinetics
In support of these applications, the applicant submitted the two bioequivalence studies under fasting conditions comparing the test products with the reference products for both strengths 50 mg and 100 mg tablets.

Study 1: Cilostazol 50 mg
This was an open-label, randomised, two-treatment, two-period, two sequences, crossover bioequivalence study comparing the pharmacokinetics of the applicant’s test product Cilostazol 50 mg Tablets (Adamed Sp. z o.o.) versus the reference product, Pletal 50 mg Tablets (Otsuka Pharmaceutical Europe Ltd.) in 45 healthy adult subjects under fasting conditions.

A single dose of the investigational products (1 tablet of 50 mg) was administered orally to each subject in each period with 240 ml of water after an overnight fast of at least 11 hours. A washout period of 14 days was maintained between the two dosing days in each group of subjects.

Serial blood sampling at Pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 14.0, 24.0, 36.0, 48.0, 60.0 and 72.0 hours post-dose was carried out in each period.

Results
Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Cilostazol 50 mg (n= 45)
Conclusion
The 90% confidence intervals for $C_{\text{max}}$ and $\text{AUC}_t$ were within the pre-defined acceptance criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**). Bioequivalence has been shown for the test formulation (Cilostazol 50 mg Tablets) and the reference formulation (Pletal 50 mg Tablets) under fasting conditions.

Study 2: Cilostazol 100 mg
This was an open-label, randomised, two-treatment, two-period, two sequences, crossover bioequivalence study comparing the pharmacokinetics of the applicant’s test product Cilostazol 100 mg Tablets (Adamed Sp. z o.o.) versus the reference product, Pletal 100 mg Tablets (Otsuka Pharmaceutical Europe Ltd.) in 47 healthy adult subjects under fasting conditions.

A single dose of the investigational products (1 tablet of 100 mg) was administered orally to each subject in each period with 240 ml of water after an overnight fast of at least 11 hours. A washout period of 14 days was maintained between the two dosing days in each group of subjects.

Serial blood sampling at Pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 14.0, 24.0, 36.0, 48.0, 60.0 and 72.0 hours post-dose was carried out in each period.

Results
Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Cilostazol 100 mg (n= 47)

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>(Ln-transformed) Geometric least squares mean</th>
<th>90% confidence interval (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test drug (T)</td>
<td>Reference drug (R)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng / mL)</td>
<td>549.551</td>
<td>572.691</td>
</tr>
<tr>
<td>$\text{AUC}_{(0-\infty)}$ (ng.h / mL)</td>
<td>8467.694</td>
<td>8711.188</td>
</tr>
<tr>
<td>$\text{AUC}_{(0-24)}$ (ng.h / mL)</td>
<td>8625.713</td>
<td>8812.944</td>
</tr>
</tbody>
</table>

Conclusion
The 90% confidence intervals for $C_{\text{max}}$ and $\text{AUC}_t$ were within the pre-defined acceptance criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**). Bioequivalence has been shown for the test formulation (Cilostazol 100 mg Tablets) and the reference formulation (Pletal 100 mg Tablets) under fasting conditions.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for applications of this type.
IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for applications of this type.

IV.5 Clinical safety
No new safety data were submitted and none were required for these applications.

IV.6 Risk Management Plan (RMP)
The Marketing Authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Cilostazol 50 and 100 mg Tablets.

A summary table of safety concerns as approved in RMP is listed as follows:

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Cardiovascular adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drug Interactions</td>
</tr>
<tr>
<td></td>
<td>Haematological adverse reactions</td>
</tr>
<tr>
<td></td>
<td>Serious bleeding events including CNS haemorrhage</td>
</tr>
<tr>
<td></td>
<td>Hepatic function disorders (including hepatitis, jaundice)</td>
</tr>
<tr>
<td></td>
<td>Renal function disorders (including renal failure)</td>
</tr>
<tr>
<td></td>
<td>Skin and subcutaneous tissue disorders (SJS and TEN)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Important Potential Risk</th>
<th>QT prolongation (serious cardiac arrhythmias)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing information</td>
<td>Off-label use</td>
</tr>
</tbody>
</table>

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Routine risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular adverse reactions</td>
<td>• Sections 4.3 and 4.4 of SPC contain transparent warnings on this risk.</td>
</tr>
<tr>
<td></td>
<td>• Sections 4.8 of the SPC address this safety concern to the prescriber adequately.</td>
</tr>
<tr>
<td></td>
<td>Additional risk minimisation measures: None</td>
</tr>
<tr>
<td>Safety Concern</td>
<td>Routine risk minimisation measures</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>• Sections 2 and 4 of the PIL also advise patients about this safety concern.</td>
</tr>
<tr>
<td></td>
<td>• Product is a prescription only medicine (POM).</td>
</tr>
<tr>
<td>Hepatic function disorders (including hepatitis, jaundice)</td>
<td>• Section 4.3 and 4.8 of the SPC address this safety concern adequate to the prescriber.</td>
</tr>
<tr>
<td></td>
<td>• Sections 2 and 4 of the PIL advise patients about this safety concern.</td>
</tr>
<tr>
<td></td>
<td>• Product is a prescription only medicine (POM).</td>
</tr>
<tr>
<td>Renal function disorders (including renal failure)</td>
<td>• Section 4.3 and 4.8 of the SPC address this safety concern adequate to the prescriber.</td>
</tr>
<tr>
<td></td>
<td>• Sections 2 and 4 of the PIL advise patients about this safety concern.</td>
</tr>
<tr>
<td></td>
<td>• Product is a prescription only medicine (POM).</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders (SJS and TEN)</td>
<td>• Section 4.8 of the SPC addresses this safety concern adequate to the prescriber.</td>
</tr>
<tr>
<td></td>
<td>• Section 4 of the PIL also advise patients about this safety concern.</td>
</tr>
<tr>
<td></td>
<td>• Product is a prescription only medicine (POM).</td>
</tr>
<tr>
<td>QT prolongation (serious cardiac arrhythmias)</td>
<td>• Section 4.3, 4.4 and 4.8 of the SPC address this safety concern adequate to the prescriber.</td>
</tr>
<tr>
<td></td>
<td>• Sections 2 and 4 of the PIL advise patients about this safety concern.</td>
</tr>
</tbody>
</table>
### IV.7 Discussion on the clinical aspects

With the exception of the bioequivalence studies, no new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

Bioequivalence has been demonstrated between the applicant’s product Cilostazol 50 and 100 mg Tablets and the reference product Pletal 50 and 100 mg Tablets (Otsuka Pharmaceutical Europe Ltd.), under fasting conditions.

The grant of Marketing Authorisations is recommended for these applications.

### V User consultation

The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet (PIL) was English.

The results show that the package leaflet meets the criteria for readability, as set out in the *guideline on the readability of the label and package leaflet of medicinal products for human use*.

### VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the products is acceptable, and no new non-clinical or clinical concerns have been identified. Bioequivalence has been demonstrated between the applicant’s products and the reference products. Extensive clinical experience with cilostazol is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Cilostazol 50 and 100 mg Tablets is presented below:
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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