National Institute of Pharmacy
Directorate
of the National Institute for Quality- and Organizational Development in Healthcare and Medicines
Budapest, Hungary

Public Assessment Report

Name of the Product:

Noclaud

50 mg and 100 mg tablets

(cilostazol)

Procedure number: HU/H/0340/001-002/DC

Marketing authorisation holder: EGIS Pharmaceuticals PLC

Date: 4 February 2014

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ration, the National Institute of Pharmacy Directorate of the National Institute for Quality- and Organizational Development in Healthcare and Medicines, the national competent authority for Human medicinal products, together with the competent authorities of the member states concerned, decided to issue the marketing authorisation of the medicinal product Noclaud 50 mg and 100 mg tablets. The marketing authorisation was granted in a decentralised procedure with Hungary as reference member state. The national competent authorities of member states concerned in this procedure: Bulgaria, Czech Republic, Latvia, Lithuania, Poland, Romania and Slovakia did agree.

The product name in Latvia and Lithuania is Sollazon.

The holder of the marketing authorisation is EGIS Pharmaceuticals PLC, Hungary.

The active substance of the tablets is cilostazol. One tablet contains 50 or 100 mg cilostazol.

The other ingredients are microcrystalline cellulose, maize starch, carmellose calcium, hypromellose 2910 and magnesium stearate.

The tablets are odourless or almost odourless, white or almost white, round, flat, bevelled edged, and

- the 50 mg tablets with stylized E engraving on one side and 601 code on the other side.
- the 100 mg tablets with stylized E engraving and 602 codes on one side and no sign on the other side.

The tablets are marketed in PVC/PVdC/Aluminium blisters in carton.

The active substance cilostazol belongs to a group of medicines called phosphodiesterase type 3 inhibitors. It has several actions which include widening of some blood vessels and reducing the clotting activity (clumping) of some blood cells called platelets inside your vessels.

Patients are prescribed Noclaud for "intermittent claudication". It is the cramp-like pain in the legs when walking and is caused by insufficient blood supply in the legs. Cilostazol can increase the distance patients can walk without pain since it improves the blood circulation in the legs. Noclaud is only recommended for patients whose symptoms have not improved sufficiently after making life-style modifications (such as stopping smoking and increasing exercise) and after other appropriate interventions. It is important that the modifications made to the life-style are maintained whilst taking cilostazol.

What should be known before taking Noclaud tablets

Do not take them if you
- are allergic to cilostazol or any of the other ingredients of this medicine;
- have the condition "heart failure";
- have persistent chest pain at rest, or have had a “heart attack” or any heart surgery in the last six months;
- have now or previously suffered from blackouts due to heart disease, or any severe disturbances of the heart beat;
- know that you have a condition which increases your risk of bleeding or bruising, such as:
  - active stomach ulcer(s),
  - stroke in the past six months.
  - problems with your eyes if you have diabetes,
  - if your blood pressure is not well controlled;
- are taking both acetylsalicylic acid and clopidogrel, or any combination of two or more medicines which can increase your risk of bleeding;
- have severe kidney disease or moderate or severe liver disease;
- are pregnant

Further warnings and precautions

Consult your doctor or pharmacist before taking Noclaud tablets:
- if you have a severe heart problem or any problems with your heart beat,
- if you have problems with your blood pressure.

During treatment with Noclaud tablets make sure that
- If you need to have surgery including having teeth removed, tell your doctor or dentist that you are taking cilostazol.
- If you experience easy bruising or bleeding, stop taking cilostazol and tell your doctor.

Noclaud tablets are not suitable for children.

Other medicines and Noclaud tablets

Inform your doctor if you take some medicines usually used to treat painful and/or inflammatory conditions of muscle or joints, or if you take medicines to reduce blood clotting.
These medicines include:
- acetylsalicylic acid,
- clopidogrel,
- anticoagulant medicines (e.g. warfarin, dabigatran, rivaroxaban, apixaban or low molecular weight heparins).

If you are taking such medicines together with Noclaud tablets your doctor may perform some routine blood tests.

Certain medicines may interfere with the effect of Noclaud tablets when taken together. They may either increase the side effects of cilostazol or make it less effective. Cilostazol may do

the same to other medicines. Before you start taking Noclaud tablets, please consult your doctor if you are taking,

- erythromycin, clarithromycin or rifampicin (antibiotics),
- ketoconazole (to treat fungal infections),
- omeprazole (to treat excess acid in the stomach),
- diltiazem (to treat high blood pressure or chest pain),
- cisapride (to treat stomach disorders),
- lovastatin or simvastatin or atorvastatin (to treat high cholesterol in the blood),
- halofantrine (to treat malaria),
- pimozide (to treat mental illnesses),
- ergot derivatives (to treat migraine, e.g. ergotamine, dihydroergotamine),
- carbamazepin or phenytoin (to treat convulsions),
- St. John's wort (a herbal remedy).

Before you start taking Noclaud tablets, please inform your doctor if you are taking medicines for high blood pressure because cilostazol may have an additional lowering effect on your blood pressure. If your blood pressure falls too low, this could cause a fast heartbeat. These medicines include:

- diuretics (e.g. hydrochlorothiazide, furosemide)
- calcium channel blockers (e.g. verapamil, amlodipine)
- ACE inhibitors (e.g. captopril, lisinopril)
- angiotensin II receptor blockers (e.g. valsartan, candesartan)
- beta blockers (e.g. labetalol, carvedilol).

Taking Noclaud tablets with food and drink

Cilostazol should be taken 30 minutes before breakfast and the evening meal.
Always take your tablets with a drink of water

Pregnancy and breast-feeding

Noclaud tablets must not be used during pregnancy and its use for breast-feeding mothers is also not recommended.

Driving and using machines

Cilostazol may cause dizziness. If you feel dizzy after taking Noclaud tablets, do not drive and do not use any tools or machines.

How to take Noclaud tablets

The recommended dose is 2 x 100 mg (two 50 mg tablets twice a day /morning and evening/ or one 100 mg tablet twice a day /morning and evening/). This dose does not need to be changed for elderly people. However, the doctor may prescribe a lower dose for those who take other medicines which may interfere with the effect of cilostazol.

Noclaud tablets should be taken 30 minutes before breakfast and the evening meal, always

with a drink of water.

The benefits of taking Noclaud tablets may be felt within 4-12 weeks of treatment. The doctor will assess the progress after 3 months of treatment and may recommend discontinuation of cilostazol if the effect of treatment is insufficient.

Cilostazol is not suitable for children.

What happens if you take more Noclaud tablets than you should?

You may have signs and symptoms such as severe headache, diarrhoea, a fall in blood pressure and irregularities of your heartbeat. Contact your doctor or your local medical institution on duty immediately. Remember to take the pack with you to clarify what medicine you have taken.

What to do if you forget to take Noclaud tablets

If you miss a dose, do not worry; wait until the next dose to take your next tablet and then carry on as normal. Do not take a double dose to make up for the forgotten tablet(s).

If you stop taking Noclaud tablets

If you stop taking cilostazol the pain in your legs may come back or get worse. Therefore, you should only stop taking Noclaud tablets if you notice side effects requiring urgent medical attention (see below) or if your doctor tells you to.

Possible side effects

Like all medicines, Noclaud tablets can cause side effects, although not everybody experiences them.

If any of the following side effects happen, you may need urgent medical attention. Stop taking Cilostazol and contact a doctor or go to the nearest hospital immediately.
- stroke
- heart attack
- heart problems which can cause shortness of breath or ankle swelling
- irregular heart beat (new or worsening)
- noticeable bleeding
- easy bruising
- serious illness with blistering of the skin, mouth, eyes and genitals
- yellowing of the skin or whites of the eyes caused by liver or blood problems (jaundice)

You should also tell your doctor immediately if you have a fever or sore throat. You may need to have some blood tests and your doctor will decide on your further treatment.

The following side effects have been reported for cilostazol:
- very common (may affect more than 1 in 10 people)

- headache,
- abnormal stools,
- diarrhoea;

- common (may affect up to1 in 10 people)
  - fast heart beat,
  - heart pounding (palpitation),
  - chest pain,
  - dizziness,
  - sore throat,
  - runny nose (rhinitis),
  - abdominal pain,
  - abdominal discomfort (indigestion),
  - feeling or being sick (nausea or vomiting),
  - loss of appetite (anorexia),
  - excessive burping or wind (flatulence),
  - swelling of ankles, feet or face,
  - rash or changes in appearance of the skin,
  - itchy skin,
  - patchy bleeding in the skin,
  - general weakness;
- uncommon (may affect up to 1 in 100 people)
  - heart attack,
  - irregular heart beat (new or worsening),
  - heart problems, that can cause shortness of breath or ankle swelling,
  - pneumonia,
  - cough,
  - chills,
  - unexpected bleeding,
  - tendency to bleed (e.g., of the stomach, eye or muscle, nose bleed and blood in spit or urine),
  - decrease in red cells in the blood,
  - dizziness on standing up,
  - fainting,
  - anxiety,
  - difficulty in sleeping,
  - unusual dreams,
  - allergic reaction,
  - muscle aches and pains,
  - diabetes and increased blood sugar,
  - stomach ache (gastritis),
  - malaise;
- rare (may affect up to1 in 1,000 people):
  - tendency to bleed for longer than usual,
  - increase in the platelets in the blood,
  - problems with the kidneys.

There may be a higher risk of bleeding into the eye in people with diabetes.

The following side effects have been reported during the use of cilostazol but it is not known how frequently they may occur (frequency cannot be estimated from the available data):

- changes in the blood pressure
- decrease in red cells, white cells and platelets in your blood
- difficulty breathing
- difficulty moving
- fever
- hot flushes
- eczema and other skin rashes
- reduced sensation of the skin
- runny or sticky eyes (conjunctivitis)
- ringing in the ears (tinnitus)
- liver problems including hepatitis
- changes in the urine.

How to store Noclaud tablets

This medicinal product does not require any special storage conditions, but keep it out of the sight and reach of children.

Scientific discussion

during the initial procedure

This module reflects the scientific discussion for the approval of Noclaud 50 mg and 100 mg tablets. The procedure was finalised at 21 November 2013. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, implemented by the Act CXV of 2005 *on Medicinal Products for Human Use and on the Amendment of Other* R*egulations Related to Medicinal Products* as well as by the Decree 52/2005 (IX. 18.) of the Minister of Health *on placing medicinal products for human use on the market* in Hungary, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Bulgaria, Czech Republic, Latvia, Lithuania, Poland, Romania and Slovakia) concerned the generic version of cilostazol 50 mg and 100 mg tablets.

The originator product has been Pletal 50 and 100 mg tablets by Otsuka Pharmaceutical Europe Ltd., U.K., authorised for marketing since 2000 in the European Union.

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Noclaud (in Latvia and Lithuania Sollazon) 50 mg and 100 mg tablets. The holder of the marketing authorisation is EGIS Pharmaceuticals PLC, Hungary.

The approved indications are as follows:

- 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);
- 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.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

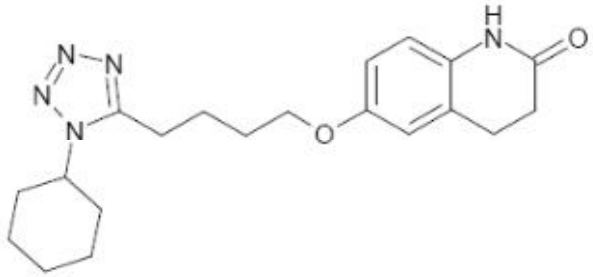
This chemical-pharmaceutical assessment report concerns the application of Noclaud 50 mg and 100 mg tablets, submitted *via* a decentralized procedure according to Article 10(1) of Directive 2001/83/EC (i.e. a generic application). The products have been developed by Egis Pharmaceuticals PLC.

The reference products are Pletal tablets 50 mg and 100 mg (containing 50 mg and 100 mg cilostazol as active ingredient) which were the original products of Otsuka Pharmaceuticals Ltd.

II.2 Drug Substance

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the Active Substance Master File (ASMF) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: cilostazol
Chemical name: 6-[4-(1-Cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydroquinolin-2(1*H*)-one
Structure:



The appearance of the active substance is white or almost white crystals. It is freely soluble in chloroform; slightly soluble in methanol and in ethanol and practically insoluble in water. It shows polymorphism, the manufacturer consistently produces the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the active pharmaceutical ingredient is adequate.

Evidence of the structure has been confirmed by NMR, MS, FT-IR, TG, XRDP and by UV spectroscopy. The impurity profile of the drug substance provides detailed information on genotoxic impurities, residual solvents and catalysts.

Cilostazol is not official in the European Pharmacopoeia (Ph. Eur.) Therefore, an in-house specification has been set for the active substance, which includes the following tests: appearance, identification by IR and HPLC, loss on drying, sulphated ash, heavy metals, related substances, residual solvents, particle size distribution and microbial purity.

The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the International Conference on Harmonisation (ICH) Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in details in the pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch-to-batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data a re-test period of 24 months is acceptable when stored in the proposed packaging not above 25°C.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal Product

The aim was to develop immediate release tablets for oral administration containing cilostazol as drug substance in 50 and 100 mg doses, which are pharmaceutically equivalent and bioequivalent to the reference medicinal product.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained:

- 50 mg strength: odourless or almost odourless, white or almost white, round, flat, bevelled edge tablets with no physical faults, no spots and no extraneous matters on the surface of tablet. The tablets are with stylized E engraving on one side and 601 code on the other side;
- 100 mg strength: odourless or almost odourless, white or almost white, round, flat, bevelled edge tablets with no physical faults, no spots and no extraneous matters on the surface of tablet. The tablets are with stylized E engraving and 602 codes on one side and no sign on the other side.

The excipients used in the finished products are microcrystalline cellulose, maize starch, carmellose calcium, hypromellose 2910, magnesium stearate. All excipients used comply with their respective Ph. Eur. monograph. Compliance of the product with the general monograph of the Ph. Eur. on the *Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is blister consisting of transparent PVC/PVdC-aluminium-foil. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 24 months with no special storage conditions is approved.

The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From chemical-pharmaceutical point of view the product is approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of cilostazol are well known.

The legal basis of the application was generic where the proof of the bioequivalence to the reference medicinal product is the requirement.

As cilostazol is a widely used, well-known active substance, the applicant has not provided additional non-clinical studies and such studies are not required. The non-clinical overview based on literature review is thus appropriate.

III.2 Pharmacology

Cilostazol is a potent inhibitor of phosphodiesterase (PDE) 3A, an isoform of PDE 3 in the cardiovascular system.

Animal studies have shown cilostazol to have vasodilator effects and this has been demonstrated in small studies in man where ankle blood flow was measured by strain gauge plethysmography. Cilostazol also inhibits smooth muscle cell proliferation in rat and human smooth muscle cells in vitro, and inhibits the platelet release reaction of platelet-derived growth factor and PF-4 in human platelets.

Studies in animals and in man (in vivo and ex vivo) have shown that cilostazol causes reversible inhibition of platelet aggregation. The inhibition is effective against a range of aggregants (including shear stress, arachidonic acid, collagen, ADP and adrenaline); in man the inhibition lasts for up to 12 hours, and on cessation of administration of cilostazol recovery of aggregation occurred within 48-96 hours, without rebound hyperaggregability.

Effects on circulating plasma lipids have been examined in patients taking cilostazol. After 12 weeks, as compared to placebo, cilostazol 100 mg b.i.d. produced a reduction in triglycerides of 0.33 mmol/L (15%) and an increase in HDL-cholesterol of 0.10mmol/L (10%).

III.3 Pharmacokinetics

Cilostazol is mostly protein bound, predominantly to albumin. The dehydro metabolite and 4'-trans-hydroxy metabolite are also protein bound.

The primary isoenzymes involved in its metabolism are cytochrome P-450 CYP3A4, to a lesser extent, CYP2C19, and to an even lesser extent CYP1A2. There are two major metabolites, the dehydro metabolite is 4-7 times as active a platelet anti-aggregant as the parent compound and the 4'-trans-hydroxy metabolite is one fifth as active.

Cilostazol is eliminated predominantly by metabolism and subsequent urinary excretion of metabolites. The primary route of elimination is urinary with the remainder excreted in the faeces. No measurable amount of unchanged cilostazol is excreted in the urine, and only a small portion of the dose is excreted as the dehydro-cilostazol metabolite. A considerable part of the dose is excreted in the urine as the 4'-trans-hydroxy metabolite. The remainder is excreted as metabolites.

The C_{max} of cilostazol and its primary circulating metabolites increase less than proportionally with increasing doses. However, the AUC for cilostazol and its metabolites increase approximately proportionately with dose.

There is no evidence that cilostazol induces hepatic microsomal enzymes.

III.4 Toxicology

Toxicological properties of cilostazol are well known. No new data submitted or needed. Non-clinical data reveal no special hazard based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

III.5 Ecotoxicity/environmental risk assessment (ERA)

The substances which may be expected to be emitted into the environment from use of this product are cilostazol and mostly its metabolites. The metabolites from the other excipients are common materials used in medications throughout the world and the incremental usage from these products is minimal. The principal route of cilostazol entering the environment in any manner is from the use and elimination by human patients. Based on this information, it can be concluded that the safety concern with cilostazol is not higher than the safety concern with the reference drug product.

Since Noclaud 50 mg and 100 mg tablets are intended for generic substitution, this will not lead to an increased exposure to the environment

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of cilostazol are well known. As it is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. The overview based on literature review is thus appropriate.

From non-clinical point of view Noclaud 50 mg and 100 mg tablets are approvable.

IV. CLINICAL ASPECTS

IV.1 Introduction

This submission concerns a generic version of cilostazol 50 mg and 100 mg tablets.

The indications of Noclaud 50 mg and 100 mg tablets are as follows:

- 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),
- 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.

Cilostazol is a potent inhibitor of phosphodiesterase (PDE) 3A, an isoform of PDE 3 in the cardiovascular system. This active substance is well known. For a generic application the proof for bioequivalence is required.

IV.2 Pharmacokinetics

IV.2.1 Literature data

Following multiple doses of cilostazol 100 mg twice daily in patients with peripheral vascular disease, steady state is achieved within 4 days.

Cilostazol is 95-98% protein bound, predominantly to albumin. The dehydro metabolite and 4'-trans-hydroxy metabolite are 97.4% and 66% protein bound respectively. Plasma concentrations (as measured by AUC) of the dehydro and 4`-trans-hydroxy metabolites are ~41% and ~12% of cilostazol concentrations.

The apparent elimination half-life of cilostazol is 10.5 hours. The two major metabolites, a dehydro-cilostazol and a 4'-transhydroxy cilostazol have similar apparent half-lives.

Cilostazol is eliminated predominantly by metabolism and subsequent urinary excretion of metabolites. The primary route of elimination is urinary (74%) with the remainder excreted in the faeces. No measurable amount of unchanged cilostazol is excreted in the urine, and less than 2% of the dose is excreted as the dehydro-cilostazol metabolite. Approximately 30% of the dose is excreted in the urine as the 4'-trans-hydroxy metabolite. The remainder is excreted as metabolites, none of which exceed 5% of the total excreted.

There is no evidence that cilostazol induces hepatic microsomal enzymes.

The pharmacokinetics of cilostazol and its metabolites were not significantly affected by age or gender in healthy subjects aged between 50-80 years.

IV.2.2 The bioequivalence study

To support the marketing authorisation submission the applicant conducted one bio-equivalence study with cross-over design under fasting conditions.

This was a standard randomised, single dose, two-treatment, two-period, open label crossover design in healthy fasting male and female subjects. The aim was to demonstrate bioequivalence of the proposed product Noclaud 100 mg tablets with the reference product and to evaluate its safety.

The reference product was Pletal 100 mg tablets (the marketing authorisation holder: Otsuka Pharmaceutical Europe Ltd., U.K., manufacturer of the batch: UCB Pharma GmbH, Germany).

Healthy, adult, Caucasian male and female non-smokers, with ages of 18 years or older, having body mass index between 18.5 and 30.0 kg/m^2 were enrolled in the study.

Concentrations of cilostazol in human plasma samples were determined using a liquid-liquid extraction procedure coupled to a HPLC-MS/MS assay developed and validated.

The pharmacokinetic parameters determined included AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, λ and $T_{½}$. Pharmacokinetic parameters were calculated using conventional non-compartmental methods. The AUC_{0-t} and C_{max} parameters were used to assess bioequivalence of test and reference (Ref) products.

ANOVA including sequence, subjects nested within sequence, period and treatment was to be performed on the ln-transformed data for AUC_t, AUC_{inf} and C_{max} and on the raw data for T_{max}, λ and $T_{1/2}$. T_{max} was to be analyzed using an additional non-parametric test (Wilcoxon test). The 90% confidence intervals (CI) of the Test/Reference ratios of geometric means for AUC_t, AUC_{inf} and C_{max} were to be calculated based on the least square means (LSMEANS) and ESTIMATE of the ANOVA. Additional statistical and alternate tests were permitted if necessary.

The results are summarised in the next Table.

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%
$AUC_{(0-t)}$	91.47	85.63 - 97.70	13.68
C_{max}	96.14	86.20 - 107.24	22.84

The results of the study show that the 90% confidence intervals for the log-transformed parameters AUC and C_{max} for cilostazol were all within the 80-125% acceptable range. Therefore, based on the submitted bioequivalence study Noclaud 100 mg tablets are considered bioequivalent to Pletal 100 mg tablets (MAH: Otsuka Pharmaceutical Europe Ltd., U.K) because the study execution and the results are compliant with requirements

of the *Guideline On The Investigation Of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev.1).

Biowaiver

The applicant has provided justification for the granting of a biowaiver for Noclaud 50 mg tablets, based on criteria set out in the current guideline on bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1):

- the 50 mg, and 100 mg strengths are manufactured by the same manufacturer site and process,
- cilostazol demonstrates linear kinetics at therapeutic doses,
- the qualitative compositions of the 50 mg and 100 mg strengths are the same,
- the composition of the 50 mg and 100 mg strengths are quantitatively proportional.

All requirements set in the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev.1) section 4.1.6 were met and biowaiver can be granted for the 50 mg tablet.

IV.3 Pharmacodynamics

No novel pharmacodynamic data were supplied or required for this application. The pharmacodynamic claims in the SPC are appropriately consistent with the innovator product.

IV.4 Clinical efficacy

No new efficacy data were supplied or required for this generic application as this application is had been made under Article 10(1) of the Directive 2001/83/EC, as amended,. However, the applicant provided a review of clinical trials published in the literature confirming the efficacy of cilostazol.

The applicant also referred the most recent EMA – CHMP document (EMA/98571/2013 - 22 March 2013 - *European Medicines Agency recommends restricting use of cilostazol-containing medicines).*

IV.5 Clinical safety

During the bioequivalence study no new safety concern appeared.

The safety profile of cilostazol is well known for the approved indications. Moreover, the applicant evaluated the safety data presented in the most important publications and in the most recent EMA – CHMP documents (*European Medicines Agency recommends restricting use of cilostazol-containing medicines*, EMA/98571/2013 - 22 March 2013 and the Art. 31 Referral SmPC).

The risk-benefit relationship is considered to be favourable provided that the prescriber takes

note of the contraindications, warnings and precautions and potential for drug interactions as detailed in the SPC.

I.1 IV.6 Discussion on the clinical aspects

The use of Cilostazol is well established. It has recognised efficacy and acceptable safety.
With regards to the current application, sufficient clinical information has been submitted which includes adequate review of published clinical data. The claim of bioequivalence to a marketed reference product can be accepted.

Therefore, from clinical point of view the overall the risk: benefit analysis for Noclaud 50 mg and 100 mg tablets is considered favourable.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The present application concerned the generic version of cilostazol 50 mg and 100 mg tablets. The applicant and the future holder of marketing authorisation was EGIS Pharmaceuticals PLC. (Hungary).

The application was submitted according to Article 10(1) of Directive 2001/83/EC.

The reference medicinal product was Pletal 50 mg and 100 mg tablets by Otsuka Pharmaceutical Europe Ltd., authorised for marketing in 2000 in the Community. The bioequivalence of the test and reference medicinal products was proven.

Cilostazol has an established favourable benefit-risk profile. The risk-benefit relationship is considered to be favourable provided that the prescriber takes note of the contraindications, warnings and precautions and potential for drug interactions as detailed in the SmPC.

With regards to the current generic application, sufficient clinical information has been submitted which includes adequate review of published clinical data.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised. The therapeutic benefit/risk assessment is, therefore, positive.

The application for Noclaud 50 mg and 100 mg tablets 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) is approvable.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Noclaud 50 mg and 100 mg tablets.

V.1 Conditions for the marketing authorisation

V.1.1 Requirements for specific post-marketing obligations

Not needed.

V.1.2 Pharmacovigilance system

The marketing authorisation holder submitted detailed description of the Pharmacovigilance System intended to be used, which fulfils the requirements and provides adequate evidence that the marketing authorisation holder has the services of qualified persons responsible for pharmacovigilance in all member states concerned and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The Risk Management Plan submitted by the applicant was acceptable.

Summary of safety concerns	
Important identified risks	-Dizziness -Hypotension -Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the Summary of Product Characteristics (SmPC). -Severe renal impairment: creatinine clearance of ≤ 25 ml/min. -Congestive heart failure. -Bleeding risk (e.g. active peptic ulceration, recent [within six months] haemorrhagic stroke, proliferative diabetic retinopathy, poorly controlled hypertension), retinal bleeding. -Cardiovascular events as ventricular tachycardia, ventricular fibrillation or multifocal ventricular ectopics, whether or not adequately treated, and in patients with prolongation of the QTc interval. -Haematological abnormalities including thrombocytopenia, leucopenia, agranulocytosis, pancytopenia and aplastic anaemia.
Important potential risks	-Co-administration with inhibitors or inducers of CYP3A4 and CYP2C19 or with CYP3A4 substrates.
Important missing information	-Pregnancy, lactation. -Use in children. -Moderate or severe hepatic impairment. -The effect of CYP3A4 and CYP2C19 inducers (such as carbamazepine, phenytoin, rifampicin and St. John's wort) on cilostazol pharmacokinetics has not been evaluated.

Summary table of risk minimisation measures	
Objective of the risk minimisation measures	Dizziness
Routine risk minimisation measures	Proposed text in SmPC. Listed in SPC section 4.8 Undesirable effects Listed in 4.7 Effects on ability to drive and use machines: Cilostazol may cause dizzi-

	ness and patients should be warned to exercise caution before they drive or operate machinery.
Objective of the risk minimisation measures	Hypotension
Routine risk minimisation measures	Proposed text in SmPC. 4.4 Special warnings and precautions for use Caution is needed when co-administering cilostazol with any other agent which has the potential to reduce blood pressure due to the possibility that there may be an additive hypotensive effect with a reflex tachycardia. Section 4.8. hypertension, hypotension, supraventricular tachycardia, ventricular tachycardia, syncope.
Objective of the risk minimisation measures	Hypersensitivity, allergic reaction
Routine risk minimisation measures	Proposed text in SmPC. Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 is listed in section 4.3 Contraindications. Allergic reaction is listed in section 4.8 Immune system disorders.
Objective of the risk minimisation measures	Severe renal impairment: creatinine clearance of ≤ 25 ml/min
Routine risk minimisation measures	Proposed text in SmPC. Renal impairment is listed in 4.2 and 4.3 of the SPC as 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. Renal failure, renal impairment as rare adverse events as well as uric acid level increased, blood urea increased, blood creatinine increased are listed in section 4.8. Undesirable effects
Objective of the risk minimisation measures	Congestive heart failure
Routine risk minimisation measures	Proposed text in SmPC: Congestive heart failure is listed in Section 4.3 Contraindications and also section 4.8 Undesirable effects.

Objective of the risk minimisation measures	Use in children
Routine risk minimisation measures	Proposed text in SmPC: 4.2 Posology and method of administration: Paediatric population The safety and efficacy of cilostazol in children have not yet been established.
Objective of the risk minimisation measures	Moderate or severe hepatic impairment
Routine risk minimisation measures	Proposed text in SmPC. Moderate or severe hepatic impairment is listed in section 4.3 Contraindications. Hepatitis, hepatic function abnormal, and jaundice are listed in section 4.8. Section 5.2 contains that there are no data in patients with moderate to severe hepatic impairment and since cilostazol is extensively metabolised by hepatic enzymes, the drug should not be used in such patients.
Objective of the risk minimisation measures	Bleeding risk
Routine risk minimisation measures	Proposed text in SmPC. Section 4.3 Contraindications contains patients with any known predisposition to bleeding (e.g. active peptic ulceration, recent [within six months] haemorrhagic stroke, proliferative diabetic retinopathy, and poorly controlled hypertension). Section 4.4 Special warnings and precautions for use Due to the platelet aggregation inhibitory effect of cilostazol it is possible that an increased bleeding risk occurs in combination with surgery (including minor invasive measurements like tooth extraction). If a patient is to undergo elective surgery and antiplatelet effect is not necessary, cilostazol should be stopped 5 days prior to surgery. Bleeding time prolonged, thrombocytopenia as rare; bleeding tendency, thrombocytopenia, cerebral haemorrhage, pulmonary haemorrhage, muscle haemorrhage, respiratory tract haemorrhage, subcutaneous haemorrhage as with unknown frequency and eye haemorrhage, epistaxis, gastrointestinal haemorrhage, haemorrhage unspecified as

	uncommon frequency are listed in the section 4.8. It is also mentioned that cilostazol per se may carry an increased risk of bleeding and this risk may be potentiated by co-administration with any other agent with such potential and the risk of intraocular bleeding may be higher in patients with diabetes. By the 4.5 Section co-administering cilostazol with any other agents that inhibit platelet aggregation (acetylsalicylic acid, clopidogrel and other antiplatelet drugs, oral anticoagulants like warfarin) may increase the possibility of hemorrhagic adverse effects, or increase bleeding time.
Objective of the risk minimisation measures	Cardiovascular events
Routine risk minimisation measures	Proposed text in SmPC. Listed in Section 4.3 Contraindications: Patients with any history of ventricular tachycardia, ventricular fibrillation or multifocal ventricular ectopics, whether or not adequately treated, and in patients with prolongation of the QTc interval. Section 4.4 Special warnings and precautions for use: Caution is needed when co-administering cilostazol with any other agent which has the potential to reduce blood pressure due to the possibility that there may be an additive hypotensive effect with a reflex tachycardia. Section 4.8. Palpitation, tachycardia, angina pectoris, arrhythmia, ventricular extrasystoles listed as common and myocardial infarction, atrial fibrillation, congestive heart failure, supraventricular tachycardia, ventricular tachycardia, syncope listed as uncommon adverse events.
Objective of the risk minimisation measures	Leucopenia, agranulocytosis, pancytopenia and aplastic anaemia
	Proposed text in SmPC. Listed in Section 4.4. Special warnings and precautions for use contains that there have been rare or very rare reports of haematological abnormalities including thrombocytopenia, leucopenia, agranulocytosis, pancytopenia and aplastic anaemia that are also

Routine risk minimisation measures	listed in see Section 4.8. It also contains that most patients recovered on discontinuation of cilostazol. However, some cases of pancytopenia and aplastic anaemia had a fatal outcome. Other signs which might also suggest the early development of blood dyscrasia such as pyrexia and sore throat. A full blood count should be performed if infection is suspected or there is any other clinical evidence of blood dyscrasia. Cilostazol should be discontinued promptly if there is clinical or laboratory evidence of haematological abnormalities.
Objective of the risk minimisation measures	Pregnancy, lactation
Routine risk minimisation measures	Proposed text in SmPC. Pregnancy is listed in the Section 4.3 Contraindications. Section 4.6 Pregnancy and lactation contains that animal data showed potential human risk and because of the lack of human data cilostazol should not be used during pregnancy. The transfer of cilostazol to breast milk has been reported in animal studies. The excretion of cilostazol in human milk is unknown. Due to the potential harmful effect in the newborn child breast fed by a treated mother, the use of Cilostazol is not recommended during breast feeding. Results of preclinical data are detailed in Section 5.3.
Objective of the risk minimisation measures	Co-administration with inhibitors or inducers of CYP3A4 and CYP2C19 or with CYP3A4 substrates
Routine risk minimisation measures	Proposed text in SmPC. It is mentioned in Section 4.4 Special warnings and precautions for use: - Co-administration of inhibitors (i.e. erythromycin, ketokonazole, diltiazem) resulted in an increase in the AUC of cilostazol. -Omeprazole (an inhibitor of CYP2C19) 40 mg once daily increased the AUC of cilostazol. - Cilostazol has been shown to increase the AUC of lovastatin (sensitive substrate for CYP3A4), caution is advised when cilostazol is co-administered with CYP3A4 substrates

	with a narrow therapeutic index (e.g., cisapride, halofantrine, pimozide, ergot derivates). Caution is advised in case of coadministration with simvastatin.
Objective of the risk minimisation measures	Cytochrome P-450 enzyme inducers
Routine risk minimisation measures	Proposed text in SmPC. It is mentioned in Section 4.4 Special warnings and precautions for use: the effect of CYP3A4 and CYP2C19 inducers (such as carbamazepin, phenytoin, rifampicin and St. John's wort) on cilostazol pharmacokinetics has not been evaluated. The antiplatelet effect may theoretically be altered and should be carefully monitored when cilostazol is coadministered with CYP3A4 and CYP2C19 inducers. In clinical trials, smoking (which induces CYP1A2) decreased cilostazol plasma concentrations by 18%.
Additional risk minimisation measure	Not proposed
Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable
Criteria for judging the success of the proposed risk minimisation measures	
Planned dates for assessment	
Results of effectiveness measurement	
Impact of risk minimisation	
Comment	The CHMP has begun looking at the benefit-risk balance of cilostazol-containing medicines, currently used to improve the maximal walking distance and maximal pain-free walking distances in patients with intermittent claudication. The safety review showed an increased risk of cardiovascular and haemorrhagic reactions. This increased risk has to be assessed in the light of a modest clinical efficacy mainly shown in a population younger than the population receiving these medicines in daily practice. (EMA/CHMP/306703/2011 See Annex 12

	Ref1) The Committee now reviewed all available data to assess the balance of benefits and risks of these medicines. With cilostazol an Art. 31 referral has been carried out with the following result on 22nd March, 2013: cilostazol should only be used in patients whose symptoms have not improved despite prior lifestyle changes such as exercise, healthy diet and stopping smoking. In addition, cilostazol-containing medicines should not be used in patients who have suffered severe tachyarrhythmia (fast, abnormal heart rhythm), or recent unstable angina, heart attack or bypass surgery, or who take two or more antiplatelet or anticoagulant medicines such as aspirin and clopidogrel. (EMA/98571/2013 See Annex 12 Ref 2)

Periodic Safety Update Report (PSUR)

Cilostazol is currently included in the list of substances under PSUR Work Sharing Scheme and other substances contained in Nationally Authorised Products with Data Lock Point synchronised (transitional list). According to this list, PSURs are required for generic medicinal products authorised under Article 10(1) of the Directive 2001/83/EC. The required PSUR cycle is 6 month long; the next data lock point is 28. 02. 2014.

Legal status

Prescription-only medicine.

V.2 Summary of Product Characteristics (SmPC)

The SmPC is, from both pharmaceutical and medical aspects, acceptable.

V.3 Package Leaflet and user testing

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 was Hungarian.

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. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached