PASS Information

Title	Cilostazol Drug Utilisation Study 2 (DUS 2) and Comparison With Drug Utilisation Study 1 (DUS 1): UK, Spain, Sweden, and Germany
Version identifier of the study report	1.0 Final
Date of study report	1 February 2017
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Active substance	Cilostazol, ATC code B01AC23, Platelet aggregation inhibitors excluding heparin
Medicinal product	Pletal, Ekistol
Product reference	UK/H/0291/001 and 002
Procedure number	EMEA/H/A-31/1306
Marketing authorisation holder(s)	Otsuka Pharmaceutical Europe Ltd Lacer S.A.
Joint PASS	No
Research question and objectives	This study has been conducted in the context of the European Medicines Agency (EMA) referral (article 31 of Council Directive 2001/83/EC) on the risks and benefits of the use of cilostazol. After recommending changes in the cilostazol summary of product characteristics (SmPC), the EMA required the conduct of two drug utilisation studies, one before implementation of the SmPC changes and a second one after implementation of the SmPC changes. The study objectives were to characterise patients using cilostazol according to demographics, comorbidity, comedications, and duration of treatment. Additional objectives were to describe the dosing of cilostazol, specialities of the prescribing physicians, and potential off-label prescribing. A first drug utilisation study (DUS 1) was conducted for the period before the implementation of changes in the 2013 SmPC. This second DUS (DUS 2) describes the characteristics of users of cilostazol after implementation of the 2013 SmPC changes and compares them with the characteristics of users in DUS 1.
Countries of study	United Kingdom, Spain, Sweden, and Germany
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Approval Page

Project Title: Cilostazol Drug Utilisation Study 2 (DUS 2) and Comparison With Drug Utilisation Study 1 (DUS 1): UK, Spain, Sweden, and Germany

Otsuka Protocol ID Number: 21-13-101

Authors:	Jordi Castellsague, MD, MPH, on behalf of the cilostazol DUS research team
	RTI Health Solutions
Report version:	1.0
Date:	1 February 2017

The following people have reviewed the study report and give their approval on behalf of the cilostazol DUS research team:

RTI Health Solutions

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1 Abstract

Title: Cilostazol Drug Utilisation Study 2 (DUS 2) and Comparison With Drug Utilisation Study 1 (DUS 1): UK, Spain, Sweden, and Germany

Keywords: cilostazol; drug utilisation study; platelet aggregation inhibitors; THIN; IACS; EpiChron; SIDIAP; GePaRD; Swedish Registries

Rationale and background: This is the second drug utilisation study (DUS 2) on the use of cilostazol in several European populations requested by the European Medicines Agency in the context of the referral Article 31 of Council Directive 2001/83/EC. In the first DUS (DUS 1), we described the characteristics of new users of cilostazol before changes in the summary of product characteristics (SmPC) were implemented in 2013. In this DUS 2, we describe the characteristics of new users of cilostazol for the year 2014, after the SmPC changes were implemented, and compare them with those evaluated in DUS 1 (before the SmPC changes).

DUS 2 has been conducted in the same populations as DUS 1: The Health Improvement Network (THIN), United Kingdom (UK); the EpiChron Cohort from the Aragón Health Sciences Institute (IACS), Aragón, Spain; the Information System for the Improvement of Research in Primary Care (SIDIAP), Catalonia, Spain; the Swedish National Health Registers, Sweden; and the German Pharmacoepidemiological Research Database (GePaRD), Germany.

This study report describes the final results of DUS 2 in all the study databases.

Research question and objectives: To evaluate the impact of the 2013 SmPC changes, characteristics of users of cilostazol where compared for the periods before (DUS 1) and after (DUS 2) implementation of the 2013 SmPC changes.

The primary objectives were to describe and compare the characteristics of new users of cilostazol by demographics, comorbidity, concurrent use of interacting medications, conditions listed in the SmPC, and discontinuation patterns, before and after implementation of the 2013 SmPC changes. Secondary objectives were to describe and compare off-label prescribing, dosage patterns, and hospitalisations in users of cilostazol, before and after the 2013 SmPC changes.

Study design: Cohort study of new users of cilostazol. Characteristics of new users were evaluated retrospectively at the start date defined as the date a patient received the first prescription or dispensing for cilostazol during the study period. New users were followed to assess treatment patterns, discontinuation, monitoring by health care practitioners, and prescriptions of comedications.

Setting: New users were defined as patients with at least 6 months of continuous enrolment in each study database who received a first-ever prescription of cilostazol between 1 January 2014 and 31 December 2014. New users were followed from the start date until the earliest of the following: end of enrolment in the database, death, or end of the study period. In DUS 1, the study period was longer than in DUS 2 in all the study databases as it involved the time since cilostazol was available in each country to the end of 2012 (end of 2011 in GePaRD).

Subjects and study size, including dropouts: A total of 7,048 patients received a prescription for cilostazol during 2014: 380 patients in THIN, 1,670 in EpiChron, 3,023 in SIDIAP, 544 in Sweden, and 1,431 in GePaRD. Of these, 1,821 patients were new users of cilostazol and were included in DUS 2: 104 new users in THIN, 367 in EpiChron, 771 in SIDIAP, 149 in Sweden, and 430 in GePaRD.

Variables and data sources: Comorbidity was identified by Read codes in THIN; the International Classification of Primary Care, Second Edition, in IACS; and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, in SIDIAP, Sweden, and GePaRD (German Modification). Procedures were identified by the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures (NCSP, version 1.16, 2012) in Sweden and by the Ambulatory and Hospital Operation or Procedure Codes in Germany. Comedications were identified by the Multilex/British National Formulary in THIN and by the Anatomical Therapeutic Chemical classification in the other databases.

Results: A total of 22,593 new users of cilostazol were included in the period before the SmPC changes (DUS 1), and 1,821 were included in the period after the SmPC changes (DUS 2). EpiChron and SIDIAP, in Spain, contributed the largest number of users in both periods. The annual prevalence of use of cilostazol decreased in all the study populations. Prevalence per 100,000 population decreased from 11.8 users (2010) to 9.9 users (2014) in THIN; from 186.5 users (2012) to 161.5 users (2014) in EpiChron; from 150.8 users (2011) to 64.7 users (2014) in SIDIAP; from 16.5 users (2010) to 7.2 (2014) users in Sweden, and from 22.8 users (2011) to 18.3 (2014) in GePaRD.

In both periods, before and after the SmPC changes, new users of cilostazol were predominantly men: from 52.3% (Sweden) to 77.3% (SIDIAP) before the SmPC changes and from 58.4% (Sweden) to 85.6% (EpiChron) after the SmPC changes.

After the SmPC changes, the median of age of new users of cilostazol decreased for both men and women in EpiChron, SIDIAP, and Sweden, but increased in THIN and GePaRD. The median of age ranged from 68.0 years (GePaRD) to 73.7 years (Sweden) before the SmPC changes and from 65.0 years (SIDIAP) to 71.0 years (THIN and Sweden) after the SmPC changes.

The proportion of users of a daily dose of 200 mg at the start date decreased after the SmPC changes in THIN (85.7% before vs. 31.7% after), EpiChron (77.3% before vs.

7.1% after), and GePaRD (87.9% before vs. 77.0% after). In Sweden, the proportion of users with a daily dose of 200 mg was similar before (78.2%) and after (79.9%) the SmPC changes. In SIDIAP, information on daily dose was not available.

The comorbidity pattern at the start date was similar before and after the SmPC changes. Cardiovascular disease was the most frequent comorbidity in both periods, followed by diabetes, skin disorders, renal diseases, and bleeding disorders. Peripheral arterial disease, hypertension, and ischaemic heart disease were the most frequent cardiovascular diseases. After the SmPC changes, the prevalence of peripheral arterial disease decreased in THIN (72.1% before vs. 64.4% after) and Sweden (55.6% before vs. 38.9% after), increased in EpiChron (36.1% before vs. 48.8% after) and SIDIAP (50.3% before vs. 79.2% after), and was similar in both periods in GePaRD.

Before and after the SmPC changes, the most frequent comedications at the start date were cardiovascular drugs, antithrombotics, proton pump inhibitors, musculoskeletal system drugs, respiratory medications, antidepressants, and drugs used in diabetes.

The proportion of users of cilostazol concurrently treated with interacting medications was similar before (82.5% to 91.6%) and after (79.0% to 91.3%) the SmPC changes. However, the proportion of users of cilostazol concurrently treated with a CYP3A4 or CYP2C19 potent inhibitor decreased after the SmPC changes in all databases and ranged from 2.7% (Sweden) to 22.3% (THIN) before the SmPC changes and from 0.7% (Sweden) to 17.3% (THIN) after the SmPC changes.

For conditions included in the new 2013 SmPC, the prevalence of current smoking at the start date increased after the SmPC changes in THIN (30.4% before vs. 37.5% after) and SIDIAP (32.3% before vs. 45.5% after), and it was approximately 15% in both periods in EpiChron. In Sweden, prevalence of smoking, evaluated through smoking-related diagnosis codes and dispensing of smoking-cessation drugs, was 3.2% before and 4.0% after the SmPC changes.

The proportion of patients with at least one visit potentially related to intermittent claudication or peripheral arterial disease in the 2 to 4 months after the start of treatment increased after the SmPC changes in THIN (49.6% before vs. 69.2% after), EpiChron (21.3% before vs. 24.2% after), and Sweden (8.5% before vs. 13.0% after), decreased in SIDIAP (53.5% before vs. 10.8% after), and was similar in both periods in GePaRD. Discontinuation of cilostazol within the first 3 months after the start of cilostazol increased after the SmPC changes in THIN (52.9% before vs. 64.4% after), SIDIAP (40.6% before vs. 58.1% after), and Sweden (39.4% before vs. 47.9% after), decreased in EpiChron (51.9% before vs. 30.4% after), and was similar in both periods in GePaRD.

The prevalence of new cardiovascular contraindications at the start date decreased in all the study populations after the SmPC changes. Prevalence ranged from 1.5% (THIN) to 11.6% (GePaRD) before the SmPC changes and from 0.3% (EpiChron) to 10.7%

(GePaRD) after the SmPC changes. After the SmPC changes, the concurrent use of cilostazol and two or more additional platelet aggregation inhibitors decreased in THIN (9.8% before vs. 3.8% after), EpiChron (13.5% before vs. 7.4% after), and Sweden (8.4% before vs. 6.7% after), and was similar in both periods in SIDIAP and GePaRD.

In the period after the SmPC changes, the rate ratio comparing the rates of visits with general practitioners and/or specialists between users at increased risk of serious cardiac events and users without increased risk decreased in THIN and EpiChron and increased in SIDIAP, Sweden, and GePaRD.

The proportion of users concurrently treated with cilostazol 200 mg per day and interacting medications decreased after the SmPC changes in all databases: from 78.7% to 27.9% in THIN, from 76.9% to 3.6% in EpiChron, from 67.5% to 63.8% in Sweden, and from 69.4% to 61.6% in GePaRD (daily dose was not available in SIDIAP). After the SmPC changes, 10 patients in Sweden (6.7%) and 31 patients in GePaRD (7.2%) were concurrently treated with a daily dose of 200 mg and interacting medications during follow-up. The daily dose was reduced in only one of these patients in GePaRD

The proportion of users concurrently treated with cilostazol 200 mg per day and CYP3A4 or CYP2C19 potent inhibitors at the start date or during follow-up decreased after the SmPC changes in all databases: from 19.6% to 5.8%% in THIN, from 10.0% to 0.0% in EpiChron, from 2.1% to 0.7% in Sweden, and from 3.6% to 1.9% in GePaRD. After the SmPC changes, there were no patients concurrently treated with a daily dose of 200 mg and CYP3A4 or CYP2C19 potent inhibitors during follow-up.

After the SmPC changes, the proportion of users considered to have received cilostazol according to the product labelling decreased in THIN (93.4% before vs. 83.7% after), and Sweden (70.2% before vs. 54.4% after), increased in EpiChron (53.6% before vs. 77.4% after) and SIDIAP (41.0% before vs. 79.2% after), and was similar in both periods in GePaRD.

Discussion: Results from this DUS 2 conducted in the UK, Spain, Sweden, and Germany indicate that the prevalence of use of cilostazol decreased in the last few years in all the study populations. In general, the characteristics of new users of cilostazol were similar before and after implementation of the 2013 SmPC changes. There was a higher proportion of men in both periods, and most users were elderly patients with a high prevalence of comorbidity, especially cardiovascular disease, and concurrent use of other medications.

Results from this DUS 2 are compatible with a positive effect of the labelling changes implemented in 2013 regarding the monitoring and early discontinuation of cilostazol, prevalence of new cardiovascular contraindications, concurrent use of two or more platelet aggregation inhibitors, and concomitant treatment of high-dose cilostazol and interacting drugs including CYP2C19 and CYP3A4 potent inhibitors. However, labelling changes did not affect the prevalence of smoking at the start of treatment or the

monitoring of patients at high cardiovascular risk in some of the study populations. On-label prescribing was lower after implementation of the 2013 SmPC changes. These findings should be interpreted with caution given the random variation introduced by the small number of cilostazol users in DUS 2, the shorter period of follow-up after SmPC changes, and the nature of the information in each of the data sources.

Marketing authorisation holder(s): Otsuka Pharmaceutical Europe Ltd and Lacer S.A.

Names and affiliations of principal/executive investigators:

- THIN: Jordi Castellsague, MD, MPH, Director, Epidemiology, RTI Health Solutions.
- EpiChron Cohort, IACS: Alexandra Prados, MD, PhD, Project Director, EpiChron Research Group on Chronic Diseases, IACS, Zaragoza, Spain.
- SIDIAP: Maria Giner-Soriano, PharmD, PhD, Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), Barcelona, Spain. Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Spain.
- Swedish National Health Registers: Marie Linder, MSc, PhD, Statistician, Centre for Pharmacoepidemiology, Unit of Clinical Epidemiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden.
- GePaRD: Oliver Scholle, MSc, Epidemiologist, Department of Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen, Germany.

The study is coordinated by RTI Health Solutions, led by Jordi Castellsague, MD, MPH, Director, Epidemiology.

The project is funded by Otsuka Pharmaceutical Europe Ltd. Otsuka has granted independent publication rights to the research team.

2 List of Abbreviations

ATC	Anatomical Therapeutic Chemical (classification)
BIFAP	Database for Pharmacoepidemiological Research in Primary Care (Base de Datos para la Investigación Farmacoepidemiológica en Atención Primària), Spain
BIPS	Leibniz Institute for Prevention Research and Epidemiology - BIPS
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMBD-AH	Hospitalisation database (Conjunt Mínim Bàsic de Dades dels Hospitals d'Aguts)
COPD	chronic obstructive pulmonary disease
CPE	Centre for Pharmacoepidemiology
CV	cardiovascular
CYP	cytochrome P-450
DDD	defined daily dose
DUS 1	first drug utilisation study
DUS 2	second drug utilisation study
EBM	Einheitlicher Bewertungsmaßstab
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GePaRD	German Pharmacoepidemiological Research Database
GP	general practitioner
HIV	human immunodeficiency virus
IACS	Aragón Health Sciences Institute, Spain
IC	intermittent claudication
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
ICD-10-GM	International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German Modification
ICPC-2	International Classification of Primary Care, Second Edition
IDIAP	Research Institute in Primary Care (Institut Universitari d'Investigació en Atenció Primària Jordi Gol), Spain
MAH	marketing authorisation holder
MEDEA	Mortality in Small Areas of Spain and Socioeconomic and Environmental Inequalities (Mortalidad en áreas pequeñas Españolas y Desigualdades Socioeconómicas y Ambientales)
MHRA	Medicines and Healthcare Products Regulatory Agency
N/A	not available
NA	not applicable
NBHW	National Board of Health and Welfare (Sweden)
NCSP	NOMESCO Classification of Surgical Procedures
NOMESCO	Nordic Medico-Statistical Committee
nQ	quarter of a calendar year
OPS	Operationen- und Prozedurenschlüssel

PAD	peripheral arterial disease
PAS	postauthorisation study
PASS	postauthorisation safety study
QC	quality control
RR	rate ratio
RTI-HS	RTI Health Solutions
SHI	statutory health insurance provider
SIDIAP	Information System for the Improvement of Research in Primary Care, Spain
SMHPA	Spanish Medicines and Health Products Agency
SmPC	summary of product characteristics
THIN	The Health Improvement Network, United Kingdom
UK	United Kingdom
USA	United States of America

3 Investigators

This drug utilisation study is conducted in five databases in four European countries and one coordinating centre.

The study databases are the following:

- The Health Improvement Network (THIN), United Kingdom (UK)
- The EpiChron Cohort, Aragón Health Sciences Institute (IACS), Spain[1]
- The Information System for the Improvement of Research in Primary Care (SIDIAP), Spain[2]
- The Swedish National Health Registers, Sweden
- The German Pharmacoepidemiological Research Database (GePaRD), Germany

The coordinating centre is RTI Health Solutions (RTI-HS) in Barcelona, Spain, and North Carolina, United States of America (USA).

A list of all investigators and contact details is included in Annex 2. The principal investigators and key study team members for each database and coordinating centre are shown below.

The Health Improvement Network (THIN), UK

THIN data were provided to RTI-HS by IMS Health, following approval of the study by the IMS Health Scientific Review Committee on 20 April 2015 and registration of the study in the EU PAS Register in March 2013.

Identification of the base study population and patients in IMS Health was overseen by Ahmed Nasser (MRPharmS, Senior Consultant), and Tahmina Ali (Medical Research Assistant) at IMS Health.

The EpiChron Cohort, Aragón Health Sciences Institute (IACS), Spain

- Principal Investigator: Alexandra Prados, MD, PhD. Project Director, EpiChron Research Group on Chronic Diseases, IACS, Zaragoza
- Project Statisticians: Beatriz Poblador, MPH; EpiChron Research Group on Chronic Diseases, IACS, Zaragoza
- Researcher: Francisca González Rubio, MD, Family Practice, EpiChron Research Group on Chronic Diseases, IACS, Zaragoza
- Researcher: Antonio Poncel Falco, MD, Health Informatics, EpiChron Research Group on Chronic Diseases, IACS, Zaragoza

[1] Instituto Aragonés de Ciencias de la Salud.
[2] Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària.

Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain

- Principal Investigator: Maria Giner-Soriano, PharmD, PhD, Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), Barcelona. Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Spain.
- Researcher: Albert Roso-Llorach, Statistician, MSc, IDIAP Jordi Gol, Barcelona. Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Spain.
- Researcher: Josep Mª Elorza, MD, Data management, Information system from SIDIAP, IDIAP Jordi Gol, Barcelona.

The Swedish National Health Registers

- Principal Investigator and Senior Adviser: Helle Kieler, MD, PhD, Associate Professor, Head, Centre for Pharmacoepidemiology, Unit of Clinical Epidemiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden
- Statistician and Project Leader: Marie Linder, MSc, PhD, Statistician, Centre for Pharmacoepidemiology, Unit of Clinical Epidemiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

The German Pharmacoepidemiological Research Database (GePaRD), Germany

- Executive Project Leader: Oliver Scholle, MSc, Epidemiologist, Department of Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen
- Statistician: Bianca Kollhorst, Department of Biometry and Data Management, Leibniz Institute for Prevention Research and Epidemiology – BIPS, Bremen

RTI Health Solutions

RTI-HS is responsible for coordinating the study across databases and for conducting the study in the THIN database.

- Principal Investigator: Jordi Castellsague, MD, MPH. Director, Epidemiology, Barcelona
- Senior Adviser: Susana Perez-Gutthann, MD, PhD, MPH. Vice President, Global Head of Epidemiology, Barcelona
- Senior Clinical Adviser and coordinator with IACS: Alejandro Arana, MD, MPH, MSC. Director Epidemiology, Barcelona
- Epidemiology Analyst: Brian Calingaert, MS, MBMA. Epidemiology Analyst, Research Triangle Park, North Carolina
- Epidemiologist: Nuria Riera, PhD. Research Epidemiologist, Barcelona
- Project Manager: Christine Bui, MPH. Research Epidemiologist, Research Triangle Park, North Carolina
- Project Manager Assistant: Anita Tormos, MPH, Barcelona

- Project Administration: Debra Crozier, AAS. Project Administrative Specialist, Research Triangle Park, North Carolina, USA

4 Other Responsible Parties

- **Study Sponsor:** Otsuka Pharmaceutical Europe Ltd; Gallions, Wexham Springs Framewood Road, Wexham; SL3 6PJ, UK

5 Milestones

The protocol version 2, dated 28 February 2013, was the protocol endorsed by the European Medicines Agency and first posted in the EU PAS Register (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) on 4 March 2013 (http://www.encepp.eu/encepp/viewResource.htm?id=14431).

The first drug utilisation study (DUS 1) was completed in 2015, and the final report, version 1.2, 31 March 2015, was approved by the Medicines and Healthcare Products Regulatory Agency (MHRA) on 20 December 2015.

Milestones for the conduct of DUS 2 are detailed in Table 1.

Table 1. Milestones for DUS2

Milestone	Anticipated Date	Actual Date
Approval of the SmPC changes	May 2013	May 2013
SmPC implementation period	Jun-Dec 2013	Jun-Dec 2013
Patient accumulation – 1 year	1 Jan 2014-31 Dec 2014	1 Jan 2014-31 Dec 2014
Data availability – THIN	1Q 2015	1Q 2015
Final report – THIN	31 Dec 2015	31 Mar 2016[a]
Data availability – EpiChron, SIDIAP, Sweden	Jan 2016	Jan 2016
Final report – THIN, EpiChron, SIDIAP, Sweden	30 Sep 2016	30 Sep 2016
Data availability – GePaRD	1 Jul 2016	1 Jul 2016
Final report – THIN, EpiChron, SIDIAP, Sweden, and GePaRD	1 Feb 2017	1 Feb 2017

GePaRD = German Pharmacoepidemiological Research Database; MHRA = Medicines and Healthcare Products Regulatory Agency; nQ = quarter of a calendar year; SIDIAP = Information System for the Improvement of Research in Primary Care database, Catalonia, Spain; SmPC = summary of product characteristics; THIN = The Health Improvement Network, United Kingdom.

[a] Delay due to the MHRA request to use the last year of data for DUS 1 in each database as the period of comparison with DUS 2 and corresponding Variation Number 85 submitted by the sponsor. The MHRA approved the Variation on 20 December 2015 and accepted use of the whole DUS 1 period as the comparator, as originally planned in the study protocol.

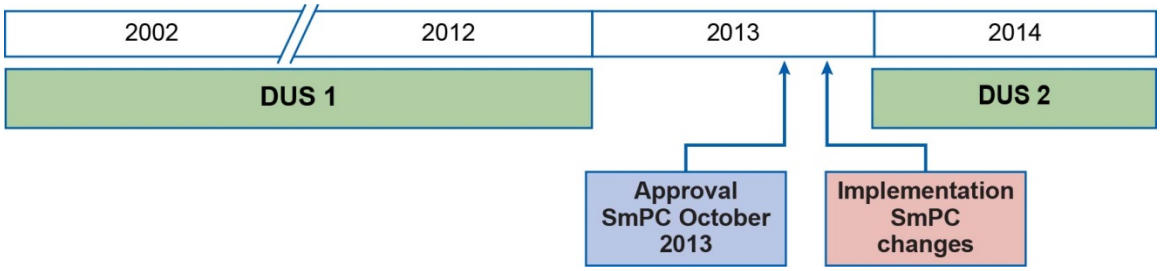
6 Rationale and Background

This is a drug utilisation study (DUS) on the use of cilostazol in several European populations in the context of the European Medicines Agency (EMA) cilostazol referral under Article 31 of Council Directive 2001/83/EC and the corresponding European Commission implementing decision (European Commission, 2013). Cilostazol has been marketed in Europe for intermittent claudication since 2002. The EMA has reviewed the role of cilostazol in current treatment of intermittent claudication and the balance of risks and benefits of the drug.

Two studies (one unpublished) conducted in Spain showed that most users of cilostazol were elderly patients with a high prevalence of comorbidity and comedications, including those potentially interacting with cilostazol (González-Ruíz et al., 2011; EMA data on file, 2012).

The EMA Rapporteur's Joint Assessment Report (4 July 2012) and the European Commission implementing decision (European Commission, 2013) required the conduct of a DUS (DUS 1) using database sources to understand the characteristics of users of cilostazol, duration and patterns of cilostazol use, and the prevalence of concomitant use of cilostazol and other drugs with which it may interact from launch to 2012. The EMA also required conduct of a second DUS (DUS 2) after the implementation of changes to the summary of product characteristics (SmPC) and the follow-up communication activities with health care professionals in 2013. The goal of DUS 2 is to assess the impact of the implementation of the risk minimisation measures by comparing the frequency of variables included in the 2013 SmPC for the period before (DUS 1) and after (DUS 2) implementation of the SmPC changes (Figure 1).

Figure 1. Study Period for DUS 1 and DUS 2 in Relation to 2013 SmPC Changes



DUS 1 = first drug utilisation study; DUS 2 = second drug utilisation study; SmPC = summary of product characteristics.

DUS 1 was completed in 2015, and the final report, version 1.2, 31 March 2015, was approved by the Medicines and Healthcare Products Regulatory Agency (MHRA) on 20 December 2015. DUS 2, completed in 2016, evaluated the use of cilostazol during 2014 using the same protocol as DUS 1.

Both DUS 1 and DUS 2 were conducted in populations covered in automated health databases from four European countries: the United Kingdom (UK), Spain, Sweden, and

Germany. This study report describes the study design, methods, and results of DUS 2 in all the study populations.

7 Research Question and Objectives

The primary objectives of DUS 1 and DUS 2 are as follows:

- To describe the characteristics of new users of cilostazol according to the following factors:
  - Demographics (e.g., age and sex)
  - Baseline comorbidity including conditions listed in the SmPC and the risk management plan as potential or identified safety concerns (Otsuka Pharmaceutical Europe Ltd., 2012)
  - Baseline and concurrent use of other medications including medications potentially interacting with cilostazol
  - Specific comorbidity and use of medications considered in the proposed risk minimisation measures, specifically those included in the proposed changes to the SmPC
- To describe the duration of use of cilostazol and discontinuation patterns

Secondary objectives of the DUS are as follows:

- To quantify and describe potential off-label prescribing
- To describe dosage patterns of the use of cilostazol
- To assess the proportion of patients who are hospitalised for any cause while treated with cilostazol
- To describe the medical specialities of physicians prescribing cilostazol

To evaluate the impact of the 2013 SmPC changes, in DUS 2 we compared the characteristics of users of cilostazol for the periods before (DUS 1) and after (DUS 2) implementation of the 2013 SmPC changes.

8 Amendments and Updates

The protocol version 2, dated 28 February 2013, was the protocol endorsed by the EMA and first posted in the EU PAS Register (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance [ENCePP]) on 4 March 2013 (http://www.encepp.eu/encepp/viewResource.htm?id=14431).

Protocol amendments are detailed in Table 2 and in Section 5 of the protocol version 2.3 dated 5 November 2015.

Table 2. Summary of Amendments and Updates

Protocol Version	Date	Section of Study Protocol	Amendment or Update	Reason
Version 2.3	5 Nov 2015	9.7.5 Assessment of Changes to the Summary of Product Characteristics	Edits for clarification; corrected typos on assessment of visits between 2 and 4 months; reduction of daily dose	Clarification and correction of typos; does not affect DUS 1 analyses
Version 2.3	5 Nov 2015	9.7.1 Number of Users and Patterns of Use	Clarification for calculating prevalence of use in DUS 2	Clarification
Version 2.3	5 Nov 2015	9.7.1 Number of Users and Patterns of Use	Evaluation of number of users with less than 12 months of continuous enrolment	MHRA request
Version 2.3	5 Nov 2015	9.2.6 Follow-up	Included date of end of follow-up	Date of end of follow-up not included in prior version
Version 2.3	5 Nov 2015	9.2.3 Study Cohort; 9.2.5 Exclusion Criteria	Added definition of new users for DUS 2	Definition of new users for DUS 2 was not included in prior version
Version 2.3	5 Nov 2015	9.2.2 Study Period	Added figure and text for the conduct of DUS 2	Clarification of study period
Version 2.3	5 Nov 2015	8 Research Question and Objectives	Added text to objectives for DUS 2	Clarification of objectives
Version 2.3	5 Nov 2015	4 Abstract; 9.3.4 Concurrent Use of Medications That May Interact With Cilostazol; 9.7.3 Use of Medications Potentially Interacting With Cilostazol; 9.7.5 Assessment of Changes to the Summary of Product Characteristics	Evaluation of potent inhibitors of CYP3A4 and CYPC19	MHRA request
Version 2.3	5 Nov 2015	4 Abstract	Clarification of reduction of daily dose	Corrected error; does not affect DUS 1 analyses
Version 2.3	5 Nov 2015	6 Milestones and Timeline	Clarification of deadline final report	Deadline is for submission of final report to the MHRA
Version 2.3	5 Nov 2015	3 Responsible Parties; 6 Milestones and Timeline	Updated acronym description for EpiChron	Change in acronym description

Protocol Version	Date	Section of Study Protocol	Amendment or Update	Reason
Version 2.2	30 Jan 2015	6.1 Milestones and Timeline for DUS 1 9.4.2 Description of Databases 10 Protection of Human Subjects	Statutory health insurance providers (SHIs) contributing data to the GePaRD, Germany	One SHI denied approval for participating in the study. Data from another SHI, with 44 users of cilostazol, were considered inadequate due to data truncation
Version 2.2	30 Jan 2015	6.1 Milestones and Timeline for DUS 1	Update status of study and preliminary reports submitted to the MHRA	Study was finalised in THIN (UK), EpiChron (Spain), SIDIAP (Spain), and Sweden, and two preliminary reports were submitted to the MHRA.
Version 2.1	30 Apr 2014	6, Milestones and Timeline	Timelines updated. Added timelines for DUS 2	Delays in the start of the study in some databases because of the conduct of preliminary analysis, contractual issues, and approvals. Revised timelines for DUS 2.
Version 2.1	30 Apr 2014	7, Rationale and Background 9.3.6, Baseline Characterisation of New Users for the Assessment of Planned Risk Minimisation Measures (SmPC Changes)	Clarifications on the conduct of DUS 2 regarding cilostazol products and study protocol	Clarifications requested by MHRA
Version 2.1	30 Apr 2014	6, Milestones and Timeline	Clarification on study report	A cumulative report summarising results from all databases will be produced
Version 2.1	30 Apr 2014	9.3.3, Characterisation of New Users at the Start Date Table 4, Diagnostic Codes for Comorbid Conditions Analysis Table 8	Categorisation of cardiovascular disease, bleeding disorders, and renal disease	To obtain more detailed information on these diseases
Version 2.1	30 Apr 2014	9.3.4, Concurrent Use of Medications That May Interact With Cilostazol Analysis Tables 10-13	Additional analysis of concurrent use of any CYP2C19 and CYP3A4 metabolisers	To assess overall use of metabolisers

Protocol Version	Date	Section of Study Protocol	Amendment or Update	Reason
Version 2.1	30 Apr 2014	9.3.5, Concurrent Use of Selected Antithrombotic Agents 9.7.4, Concurrent Use of Antithrombotic Agents Analysis Tables 14-15	Analysis conducted during consecutive use of cilostazol instead of current use of cilostazol. Corrected codes for some antithrombotic agents	Consecutive use of cilostazol reflects better its chronic use according to descriptive analysis of consecutive prescriptions
Version 2.1	30 Apr 2014	9.3.6, Baseline Characterisation of New Users for the Assessment of Planned Risk Minimisation Measures (SmPC Changes) 9.7.5, Assessment of Changes to the Summary of Product Characteristics Analysis Tables 17B and 17C	Changes of period of assessment of visits (2-4 months after start date instead of 3-4 months). Unplanned analysis of visits between 1 and 6 months after start date. Unplanned analysis of visits using diagnosis/visit codes	To improve assessment of visits based on clinical review of patient profiles
Version 2.1	30 Apr 2014	9.3.6, Baseline Characterisation of New Users for the Assessment of Planned Risk Minimisation Measures (SmPC Changes) 9.7.5, Assessment of Changes to the Summary of Product Characteristics Analysis Table 17A	Assessment of discontinuation of cilostazol by survival analysis	Survival analysis used to take into account censoring
Version 2.1	30 Apr 2014	9.3.6, Baseline Characterisation of New Users for the Assessment of Planned Risk Minimisation Measures (SmPC Changes)	Analysis of reduction of dose conducted during consecutive use of cilostazol instead of current use of cilostazol	Consecutive use of cilostazol reflects better its chronic use according to descriptive analysis of consecutive prescriptions
Version 2.1	30 Apr 2014	9.3.6, Baseline Characterisation of New Users for the Assessment of Planned Risk Minimisation Measures (SmPC Changes) 9.7.7, Overall Assessment of Contraindications Analysis Table 28	Overall assessment of labelled and new 2013 SmPC contraindications	To assess overall number of users with any contraindication for cilostazol
Version 2.1	30 Apr 2014	9.7.1, Number of Users and Patterns of Use Analysis Table 29	Distribution of users by the number of prescriptions received	Additional analysis

Protocol Version	Date	Section of Study Protocol	Amendment or Update	Reason
Version 2.1	30 Apr 2014	9.7.1, Number of Users and Patterns of Use Analysis Table 30	Distribution of users by the year of start date	Additional analysis
Version 2.1	30 Apr 2014	9.7.1, Number of Users and Patterns of Use Analysis Table 25	Age- and sex-specific prevalence of use	Additional analysis
Version 2.1	30 Apr 2014	9.7.1, Number of Users and Patterns of Use Analysis Table 31	New analysis table for calculation of mean of age by sex	To document results of analysis
Version 2.1	30 Apr 2014	9.7.2, Characterisation of Users at the Start Date Analysis Table 24	New analysis table	To document results of analysis
Version 2.1	30 Apr 2014	9.7.3, Use of Medications Potentially Interacting With Cilostazol Analysis Table 27	Distribution of users by the number of interacting medications received	Additional analysis
Version 2.1	30 Apr 2014	PASS Information	Included EU PAS Register number	Protocol submitted and EU PAS Register number obtained
Version 2.1	30 Apr 2014	Marketing Authorisation Holder(s)	Updated sponsor address and contact person	Changes in Otsuka organisation
Version 2.1	30 Apr 2014	Approval page	Updated Otsuka approval person	Changes in Otsuka organisation
Version 2.1	30 Apr 2014	3 Responsible Parties	Updated information	Changes in Otsuka organisation and confirmation of collaborating institutions

DUS = drug utilisation study; EU PAS Register = European Union electronic register of post-authorisation studies; GePaRD = German Pharmacoepidemiological Research Database; MHRA = Medicines and Health Products Regulatory Agency; PASS = postauthorisation safety study; SHI = statutory health insurance provider; SIDIAP = Information System for the Improvement of Research in Primary Care, Spain; SmPC = summary of product characteristics; THIN = The Health Improvement Network, United Kingdom; UK = United Kingdom.

9 Research Methods

9.1 Study Design

These drug utilisation studies (DUS 1 and DUS 2) are cohort studies of new users of cilostazol identified in five European population-based automated health databases in Spain, the UK, Germany, and Sweden. New users of cilostazol were defined as patients with at least 6 months of continuous enrolment in the study databases who received a first-ever prescription or dispensing of cilostazol. Information on the use of cilostazol was based on prescriptions in THIN (The Health Improvement Network, United Kingdom); on dispensings in the EpiChron Cohort, Sweden, and Germany; and on prescriptions and dispensings in SIDIAP (Information System for the Improvement of Research in Primary Care, SPAIN). For simplification, we use the term prescriptions when referring to all databases.

New users of cilostazol were characterised in terms of demographics, comorbidity, and past and concurrent use of medications before and after the date of receiving the first prescription for cilostazol, defined as the start date (Table 3).

Table 3. Timing of Assessment of Characteristics of New Users of Cilostazol

Characteristics	Time of Assessment
Comorbidities	Any time before start date
Comedications	6 months before start date
Conditions and procedures to evaluate risk minimisation measures	6 months before start date
Potentially interacting medications	3 months before start date and during follow-up

The characteristics of new users of cilostazol were compared between the period before (DUS 1) and the period after (DUS 2) the implementation of the 2013 SmPC changes.

9.2 Setting

The study was conducted in the following population-based automated health databases and countries:

- The Health Improvement Network (THIN), UK
- The EpiChron Cohort, the Aragón Health Sciences Institute (IACS), Spain[1]
- The Information System for the Improvement of Research in Primary Care (SIDIAP) database in Catalonia, Spain[2]
- The Swedish National Health Registers
- The German Pharmacoepidemiological Research Database (GePaRD), Germany

[1] Instituto Aragonés de Ciencias de la Salud.
[2] Sistema d'Informació per el Desenvolupament de la Investigació en Atenció Primària.

9.3 Subjects

In each study database, the cohort of new users of cilostazol included all individuals who received a first-ever prescription of cilostazol during the study period after having at least 6 months of continuous enrolment in the database. The date of the first cilostazol prescription was defined as the start date. Each member of the study cohorts was followed from the start date until the first of the following termination dates: end of enrolment in the database, death, or end of the study period.

For DUS 1, the study period was defined in each database as the time between the date when cilostazol became available in the corresponding country and the latest date of data availability. For DUS 2, the study period in all databases was from 1 January 2014 through 31 December 2014 (Table 4).

Table 4. DUS 1 and DUS 2 Study Period by Database

Database	Study Period DUS 1	Study Period DUS 2
THIN, UK	29 Jul 2002-14 Sep 2012	1 Jan 2014-31 Dec 2014
EpiChron, Spain	1 Jun 2009-31 Dec 2012	1 Jan 2014-31 Dec 2014
SIDIAP, Spain	1 Jun 2009-31 Dec 2012	1 Jan 2014-31 Dec 2014
Sweden	20 Mar 2008-31 Dec 2012	1 Jan 2014-31 Dec 2014
GePaRD, Germany	1 Jan 2007-31 Dec 2011	1 Jan 2014-31 Dec 2014

DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; SIDIAP = Information System for the Improvement of Research in Primary Care database, Catalonia, Spain; THIN = The Health Improvement Network, United Kingdom.

9.4 Variables

9.4.1 Utilisation Patterns

The total number of users, prescriptions, and defined daily doses of cilostazol were described by strength, quantity prescribed, and year of the start date. Daily dose at the start date was evaluated by age and sex. Daily dose of cilostazol was calculated using the recorded information on strength, quantity prescribed, dosage instructions, and days of supply of each prescription.

When dosage instructions were not available, daily dose was imputed from the median specific to the corresponding strength and quantity prescribed (THIN). In Sweden, daily dose was calculated assuming a twice-daily dosage according to the results of a manual review of free text associated with dispensings. A twice-daily dosage was also assumed in GePaRD. In SIDIAP, information on daily dose was not available because the exact day of dispensings is not recorded in the database.

Current use of cilostazol was defined as starting on the prescription date and continuing through the time covered by the days of supply of each prescription plus 7 days to allow for a potential delay in the start of treatment. Days of supply were estimated from the quantity prescribed and dosage instructions or from a descriptive analysis of the time between consecutive prescriptions. In Sweden and GePaRD, days of supply were calculated as the number of tablets dispensed divided by 2, assuming a twice-daily dosage.

Continuous use of cilostazol was defined as the total number of days covered by all periods of consecutive prescriptions, which was defined as prescriptions with a maximum interval of 60 days between the end of days of supply of the first prescription (plus 7 days, except in SIDIAP where the exact number of days is unknown) and the date of the next prescription. Sensitivity analyses were conducted for a maximum interval of 90 days between prescriptions.

9.4.2 Characterisation of Users

New users of cilostazol were characterised at the start date according to age, sex, history of smoking, social class, and year of start date in DUS 1; comorbidity at any time before the start date; and use of medications within 6 months before the start date.

Comorbidity was evaluated using Read codes in THIN, using the International Classification of Primary Care, Second Edition (ICPC-2) in the EpiChron Cohort, and using the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) in SIDIAP, Sweden, and Germany (German Modification). Procedures were ascertained by Read codes in THIN, by NOMESCO (Nordic Medico-Statistical Committee) Classification of Surgical Procedures (NCSP, version 1.16, 2012) in Sweden, and by Ambulatory and Hospital Operation or Procedure Codes in Germany. Procedures codes were not available in the EpiChron Cohort and SIDIAP. Use of medications was assessed in THIN using Multilex/British National Formulary codes mapped to the Anatomical Therapeutic Chemical (ATC) classification (see list of codes in separate files THIN1 and THIN2) and in the rest of databases using ATC codes.

In THIN, social class was evaluated using the Townsend deprivation index based on geographic area linkage of households. The scores were grouped in quintiles from 1, least deprived, to 5, most deprived (Morris and Carstairs, 1991; Townsend et al., 1988). In SIDIAP, social class was evaluated using the MEDEA[1] deprivation index (Domínguez-Berjón et al., 2008). In Sweden, information on social class was based on the family income classified in quartiles, and education level was based on number of years of education. Information on social class was not available in the EpiChron Cohort and GePaRD.

[1] MEDEA = Mortality in Small Areas of Spain and Socioeconomic and Environmental Inequalities.

9.4.3 Concurrent Use of Potentially Interacting Medications

Cilostazol may interact with cytochrome P-450 (CYP) enzymes, particularly CYP3A4 and CYP2C19. We evaluated the concurrent use of cilostazol and CYP3A4 and CYP2C19 substrates and inhibitors and CYP3A4 inducers (Trustees of Indiana University, 2013). Concurrent use was evaluated at the start date and during follow-up. Concurrent use at the start date was defined as having a prescription for an interacting medication within 3 months before the start date. Concurrent use during follow-up was defined as having a prescription for an interacting medication during the periods of continuous use of cilostazol.

9.4.3.1 Concurrent Use of CYP3A4 and CYP2C19 Potent Inhibitors

In addition, we evaluated the concurrent use of CYP3A4 and CYP2C19 potent inhibitors. Potent inhibitors were selected according to the Indiana Classification (Trustees of Indiana University, 2013) and the United States Food and Drug Administration Drug Development and Drug Interactions.[1] Potent inhibitors were lansoprazole, fluvoxamine, nefazodone, ticlopidine, clarithromycin, troleandomycin, indinavir, ritonavir, nelfinavir, mibefradil, ketoconazole, and itraconazole.

9.4.4 Concurrent Use and Discontinuation of Antithrombotic Agents

Concurrent use of antithrombotic agents including other platelet aggregation inhibitors was evaluated at the start date and during continuous use of cilostazol. Concurrent use was defined as any person-time overlapping continuous use of cilostazol and continuous use of antithrombotic agents. Continuous use of antithrombotic agents was defined in the same way as continuous use of cilostazol.

Discontinuation of platelet aggregation inhibitors after starting cilostazol was evaluated among patients concurrently using cilostazol and platelet aggregation inhibitors at the start date. Discontinuation was defined as not having a recorded prescription for a platelet aggregation inhibitor within 60 days after the end of days of supply of the prior prescription. Sensitivity analyses were conducted assuming 30 days and 90 days after the end of days of supply of the prior prescription.

9.4.5 Characterisation of Users for the Assessment of SmPC Changes

Users of cilostazol were characterised according to (1) the labelling prior to the 2013 SmPC changes and (2) the new labelling with the 2013 SmPC changes required by the EMA (Table 5).

[1] http://medicine.iupui.edu/clinpharm/ddis/clinical-table/ (accessed February 2015)
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm (accessed February 2015)

Table 5. 2013 Changes in the Labelling of Cilostazol

2013 Changes to the Summary of Product Characteristics	
Restricted target population	
Indication	Second-line use after lifestyle modifications, including smoking cessation and (supervised) exercise programmes, failed to sufficiently improve symptoms
	Physician reassessment of patients after 3 months of treatment with a view to discontinuing cilostazol where an inadequate effect is observed
Contraindications	Unstable angina pectoris, myocardial infarction within the last 6 months, or a coronary intervention in the last 6 months
	Concomitant treatment with two or more additional platelet aggregation inhibitors (e.g., aspirin, clopidogrel)
Other changes	
Warnings and precautions	Close monitoring of patients at increased risk for serious cardiac adverse events as a result of increased heart rate, e.g., patients with stable coronary disease or a history of tachyarrhythmias
Posology	Reduction of the dose to 50 mg twice daily in patients receiving medicines that strongly inhibit CYP3A4 or CYP2C19

In the following sections, we describe the variables evaluated.

9.4.5.1 Changes in Indication

- Smoking status at the start date. Smoking status was not available in Sweden and Germany. In Sweden, smoking status was approached using diagnosis codes for smoking-related disease and use of smoking-cessation drugs.
- Monitoring of patients after 3 months of starting treatment, to assess discontinuation of cilostazol because of inadequate effects.

Monitoring after 3 months was evaluated by the number of patients who had at least one visit to the general practitioner (GP) or to a specialist (cardiologist, vascular specialist, diabetologist) between 2 months and 4 months after the start date. Visits to the specialists were considered related to peripheral arteriopathy. A sensitivity analysis was conducted evaluating visits between 1 month and 6 months after the start of treatment. In Sweden, visits were assessed through hospital inpatient and outpatient discharge codes because data on primary care were not available. In GePaRD, the number of visits is not recorded, and the speciality of the physician (GP or specialist) recording the diagnosis may be inaccurate. Also, diagnoses in GePaRD are recorded on a quarterly basis. Therefore, the number of patients monitored was evaluated by the number of patients who had at least one diagnosis for intermittent claudication recorded in the quarter following the quarter in which cilostazol was started. A sensitivity analysis was conducted to evaluate diagnoses in the two calendar quarters following the start date.

In addition, in THIN (UK) and SIDIAP (Spain), we assessed the reason for the visits to the GPs and specialists by clinically reviewing the computerised information and free text of patient records (patient profiles). For DUS 1, we reviewed the patient profiles for a

random sample of 200 patients in both THIN and SIDIAP. For DUS 2, we reviewed the patient profiles of all patients included in THIN. Free text for DUS 2 was not available in SIDIAP. In THIN, the clinical review of patient profiles and free text was conducted by Dr. Jordi Castellsague, after conducting a joint review of a few profiles with Dr. Cristina Varas-Lorenzo (cardiologist). In SIDIAP, the clinical review of patient profiles and free text was conducted by Dr. Maria Giner-Soriano. Free text from GPs was not available in the rest of databases.

- Discontinuation of cilostazol after 3 months. This variable was used as a proxy for lack of efficacy of cilostazol. Discontinuation was defined as the end of the first period of continuous use of cilostazol (i.e., having an interval greater than 60 days between the end of supply of a prescription and the date of the next prescription).

9.4.5.2 Changes in Contraindications

Contraindications in Labelling Prior to 2013 SmPC Changes

- Contraindications included in the SmPC since approval of cilostazol are severe renal impairment, moderate to severe hepatic impairment, congestive heart failure, history of bleeding disorders, and history of arrhythmias. History of bleeding disorders included active peptic ulcer, recent haemorrhagic stroke, proliferative diabetic retinopathy, and poorly controlled hypertension. Poorly controlled hypertension was only evaluated in SIDIAP (Spain) where values on blood pressure are recorded for all patients. History of arrhythmias included ventricular tachycardia, ventricular fibrillation or multifocal ventricular ectopics, and prolongation of the QT interval (not available in GePaRD). Codes used to ascertain these contraindications are presented in file THIN2 for THIN and the file CODES for the rest of databases.

  Active peptic ulcer and recent haemorrhagic stroke were evaluated by diagnoses recorded within the 6 months before the start date. The rest of the contraindications were assessed by diagnoses recorded at any time before the start date.

New Contraindications

- Unstable angina pectoris, myocardial infarction, or coronary intervention within 6 months before the start date.
- Concurrent use of cilostazol and two or more additional platelet aggregation inhibitors. Concurrent use was defined as any person-time overlapping continuous use of cilostazol and continuous use of two or more additional antithrombotic agents. Concurrent use was ascertained at the start date and during continuous use of cilostazol.

9.4.5.3 Changes in Warnings and Precautions

- Monitoring of patients at increased risk of serious cardiac events. Rates of visits to the GP or specialists were used as a proxy for intensified monitoring and were

compared between patients with history of arrhythmias, hypotension, or coronary heart disease and patients without history of these conditions. In GePaRD, number of visits is not recorded, and monitoring was evaluated by using the number of quarters a patient had a diagnosis for intermittent claudication recorded during continuous use of cilostazol. This was expressed as the number of quarters per person per year and was reported as number of diagnoses per patient-year of continuous use.

9.4.5.4 Changes in Posology

- Reduction of daily dose in patients receiving medications interacting with CYP3A4 or CYP2C19 enzymes. Daily dose of cilostazol was assessed among concurrent users of cilostazol and medications interacting with CYP3A4 or CYP2C19. An additional analysis was conducted to evaluate CYP3A4 and CYP2C19 potent inhibitors. Daily dose was evaluated at the start date and after the initiation of an interacting medication during continuous use of cilostazol. Concurrent use was defined as any patient who had a prescription for an interacting medication within 3 months before the start date or during the period of continuous use of cilostazol.
- In SIDIAP, reduction of daily dose was not evaluated because the exact day of dispensing is not recorded in the database.

9.4.6 Indication and Off-Label Use

The potential indication and off-label use of cilostazol was evaluated in all users of cilostazol using hospital (inpatient) and outpatient discharge codes. On-label prescribing of cilostazol was defined as follows:

- Patients with a diagnosis for atherosclerosis/peripheral vascular disease recorded before or on the start date or during follow-up, or
- Patients with a referral to angiology or vascular surgery within 1 month before or 1 month after the start date or during the time of continuous use of cilostazol

In THIN (UK), for DUS 1 the evaluation of the indication and potential off-label use of cilostazol was conducted through clinical review of the computerised clinical information and free-text information (patient profiles) of a random sample of 200 patients. Patients were identified through simple random sampling by age (< 70 years and ≥ 70 years) and strength of first prescription (50 mg or 100 mg). The review of patient profiles was conducted by Dr. Jordi Castellsague and Dr. Cristina Varas-Lorenzo. In a first step, both investigators reviewed independently the same 25 patient profiles. Results from this first review were discussed and a template to collect the relevant information was agreed and designed. In a second step, the rest of the profiles were split between the two investigators and a single review of each profile was conducted. Finally, all profiles from each set with potential off-label prescribing of cilostazol were discussed and agreed by the two investigators. For DUS 2, the clinical review of patient profiles was conducted for all patients included in the study. The review was conducted by Dr. Jordi Castellsague.

In the EpiChron Cohort (Spain) and Sweden, free-text comments from GPs were not available, and evaluation of the indication was conducted using diagnostic codes for peripheral vascular disease and referrals to vascular surgery.

In SIDIAP (Spain), for DUS 1 the indication was evaluated by review of the computerised information and free text in a random sample of 200 patients. The review was conducted by Dr. Maria Giner-Soriano. Free text in SIDIAP was not available for DUS 2.

In Germany, off-label use was evaluated by using inpatient diagnosis codes recorded in the period 28 days before and 28 days after the start date and outpatient diagnosis codes and physician specialties in the period involving the quarter before and the quarter after the start date. A sensitivity analysis was conducted ascertaining diagnosis at any time before and after the start date.

9.4.7 Hospitalisations

Number of patients hospitalised during continuous use of cilostazol.

9.4.8 Speciality of Prescribers

In THIN (UK), the EpiChron Cohort, and SIDIAP (Spain), the specialty of prescribers of medications is not recorded in the databases and could not be evaluated. In Sweden, the medical department of prescribers, but not the specific speciality, was available. In Germany, the speciality of prescribers was available and is described.

9.5 Data Sources and Measurement

9.5.1 The Health Improvement Network (THIN), UK

Established in 2002, THIN collects data from more than 400 health care practices in the UK, covering about 6% of the general population (Cegedim Strategic Data Medical Research UK, 2012). THIN records information on all services provided by GPs including diagnoses and prescribed medications and information the GPs receive from hospital admissions and outpatient specialist visits. Prescriptions from specialists are not captured in THIN. However, all treatments initiated by a specialist are continued by the GP after the first prescription. Diagnoses are recorded using Read codes, and medications are recorded using Multilex/British National Formulary codes. The THIN database has been shown to be representative of the UK population (Blak et al., 2011) and has been validated as accurately recording a patient's health care (Denburg et al., 2011). Pharmacoepidemiologic studies using THIN data have been published in scientific journals (e.g., Choi et al., 2012; Hayes et al., 2011).

9.5.2 The EpiChron Cohort, Aragón Health Sciences Institute (IACS), Aragón, Spain

A group of researchers in Public Health and Health Services Research of IACS has linked the electronic medical and administrative databases in the region. These databases contain administrative and clinical information from outpatient clinics (primary care health centres), speciality clinics, emergency departments, hospitals, and pharmacies. From 2010 onwards, data are available for 1.2 million patients covered by all outpatient practices in Aragón. The following types of data are available: administrative and clinical information from outpatient clinics (primary care health centres), administrative and clinical information from speciality clinics, emergency department diagnoses and care, hospital procedures and discharge diagnoses, and prescription and pharmacy data. Studies are conducted in collaboration with the Instituto de Investigación Sanitaria Aragón (IIS Aragón).

9.5.3 The Information System for the Improvement of Research in Primary Care (SIDIAP), Catalonia, Spain

SIDIAP currently collects information from 274 primary health care centres, including more than 5.8 million patients, about 80% of the Catalan population covered by the Catalan Institute of Health (Bolíbar et al., 2012). Primary care physicians with an up-to-standard quality of care provide information on approximately 1.9 million patients (García-Gil et al., 2011). Information from different data sources can be accessed through linkage by an individual's national security number, including demographic information from the Catalan Health Services database, electronic primary care clinical and laboratory test records, drugs dispensed in community pharmacies, hospital discharge codes from an external hospital database (Conjunt Mínim Bàsic de Dades dels Hospital d'Aguts [CMBD-AH]), date of death from the National Office of Statistics, and other available disease or procedural registries. Availability of pharmacy-dispensed drug information is available since 2005.

9.5.4 The Swedish National Health Registers, Sweden

In Sweden, the national health care system provides universal coverage to all residents (9.7 million inhabitants[1]). Health care coverage includes visits to GPs, specialists, hospital admissions, and hospital outpatient visits; drug costs are either partially or completely covered. A centralised civil registration system has been in place since 1947. A personal identification number (9 digits since 1947 and 10 digits since 1967) allows for personal identification of each person in the entire population and for the possibility of linkage to all national registers containing civil registration numbers (Furu et al., 2009).

[1] Population data from Eurostat. 2015. Available at: http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=demo_pjan&lang=en. Accessed 8 November 2016.

The National Patient Register covers all publicly run inpatient care in Sweden from 1987 and includes information on diagnoses and surgical procedures. Since 1997, diagnoses have been coded using ICD-10 codes. Visits to GPs and specialists outside the hospitals are not included in the registers. Data collected in these registers can be made available for research purposes under the principles for protection and release of sensitive data (Ludvigsson et al., 2011). The Swedish Prescribed Drug Register provides patient-level data on all dispensed prescribed drugs (reimbursed and non-reimbursed) in ambulatory care to the whole population of Sweden since July 2005.

9.5.5 The German Pharmacoepidemiological Research Database (GePaRD), Germany

GePaRD is a population-based database obtained from statutory health insurance providers (SHIs) in Germany (Jobski et al., 2012; Kraut et al., 2010; Pigeot and Ahrens, 2008). Ninety percent of the population in Germany is insured with the SHIs. The database covers over 20 million SHI members from all regions of Germany, approximately 20% of the German population. Membership in SHIs is fairly stable over time. GePaRD includes individual information on demographics, hospital diagnoses and procedures, ambulatory care diagnoses and procedures, and ambulatory prescriptions including date of prescription and date of pharmacy dispensing. The German version of the ICD-10 (ICD-10-GM) is used for coding diagnoses, and OPS (Operationen- und Prozedurenschlüssel) codes are used for surgical and diagnostic procedures. Types of treatments and diagnostic procedures with exact date are registered according to EBM (Einheitlicher Bewertungsmaßstab) codes, developed for payment of physicians for the outpatient treatment of German SHI patients.

9.6 Bias

DUS 1 included a large number of users as the study period covered several years in each database. However, the study size for DUS 2 was smaller because the study was restricted to new users identified during the year 2014. Thus, random variability should be taken into account when interpreting the results for DUS 2. Also, the follow-up of new users of cilostazol after SmPC changes was limited to a maximum of 12 months. This could result in underascertainment of variables measured during follow-up.

THIN includes detailed information on the prescriptions issued by GPs only. Prescriptions initiated by specialists are not recorded, although most of them are continued by the GP. If a first prescription for cilostazol was issued by a specialist (e.g., vascular surgery), that first prescription was not captured in the database. This could introduce misclassification on the date of starting of cilostazol and/or exclusion of patients who did not continue the use of cilostazol after that first prescription. Information on prescriptions for the rest of databases was based on dispensed medications.

Although health habits such as cigarette smoking are usually recorded in the THIN, SIDIAP, and EpiChron databases, the prevalence of smoking may have been underestimated as the recording may be incomplete. In the GePaRD and the Swedish registers, smoking habits are not recorded. In Sweden, the evaluation of smoking was based on the dispensing of smoking-cessation drugs and the recording of diagnoses related to smoking. This led to underestimation of the prevalence of smoking. For the contraindication of "poorly controlled hypertension," blood pressure values were available in SIDIAP but not in the rest of the study populations. Therefore this contraindication was only evaluated in the SIDIAP population. Prevalence of use of prescription medications that were also available over the counter may have been underestimated since over-the-counter drugs are not captured in the databases included in this study.

Free-text comments to evaluate monitoring visits after the start of cilostazol were available only in THIN and SIDIAP for DUS 1 and only in THIN for DUS 2. In the rest of the databases, monitoring visits were conducted through diagnoses recorded by GPs and specific specialists (e.g., vascular surgery) and visit codes (THIN). In GePaRD, only diagnoses related to intermittent claudication were used, because the speciality of the physicians recording diagnoses is inaccurate. This most probably led to an underestimate of the intensity of monitoring after the start of cilostazol.

Similarly, off-label prescribing was evaluated using free-text comments in THIN and SIDIAP for DUS 1 and only in THIN for DUS 2, but not in the other databases. This could lead to an overestimate of potential off-label prescribing of cilostazol in EpiChron, Sweden, and GePaRD, as the indication of cilostazol may be underrecorded in these databases.

9.7 Study Size

The study included all new users of cilostazol available in the study populations in each study period: before (DUS 1) and after (DUS 2) the SmPC changes. The study cohort in THIN included 1,528 new users of cilostazol in DUS 1 and 104 new users in DUS 2. Data from EpiChron included the population of Aragón in Spain covered by all primary care practices and included 4,024 new users in DUS 1 and 367 new users in DUS 2. Data from SIDIAP covered approximately 80% of the population of Catalonia in Spain covered by primary care practices and included 10,142 new users of cilostazol in DUS 1 and 771 new users in DUS 2. Data from Sweden involved the entire population of Sweden and included 2,887 new users of cilostazol in DUS 1 and 149 new users in DUS 2. Data from Germany in DUS 1 included 4,012 patients covered in two SHIs providing data to GePaRD. DUS 2 in GePaRD will cover one SHI (data for a small SHI included in DUS 1 were not available for inclusion in DUS 2).

9.8 Data Transformation

THIN, UK: Files from THIN were received at RTI Health Solutions (RTI-HS), quality checked, and integrated for the overall study cohort. For selected patients, computerised information was formatted into patient profiles for clinical review. At second step, free text was integrated. Categorical variables were created based on the variables definitions.

EpiChron, Aragón, Spain: Files from the Aragón department of health were received at IACS, quality checked, and integrated for the overall study cohort. For selected patients, computerised information was formatted into patient profiles for clinical review. Categorical variables were created based on the variables definitions.

SIDIAP, Catalonia, Spain: Files from the Catalan Health Institute were received at the Research Institute in Primary Care, Spain (IDIAP), quality checked and integrated for the overall study cohort. For selected patients, computerised information was formatted into patient profiles for clinical review. At second step, free text was integrated. Categorical variables were created based on the variables definitions.

National Registers, Sweden: Files from the National Board of Health and Welfare (NBHW) and Statistics Sweden were received at the Centre for Pharmacoepidemiology (CPE), Department of Medicine, Karolinska Institutet, where they were quality checked and integrated for the overall study cohort. Before delivery to the CPE, the NBHW anonymised data by replacing personal identification numbers with a running number. Categorical variables were created by the CPE based on the variables definitions.

GePaRD: Files from SHIs providing data to GePaRD were received at the Leibniz Institute for Prevention Research and Epidemiology (BIPS), quality checked, and integrated in the analytical study data set.

9.9 Statistical Methods

9.9.1 Main Summary Measures

Number and proportion of patients with a specific characteristic.

9.9.2 Main Statistical Methods

In DUS 1, the average annual prevalence of use of cilostazol was calculated using the age and sex distribution of each specific database (year 2008 in THIN, year 2011 in EpiChron, year 2012 in SIDIAP, and year 2009 in GePaRD). In Sweden, the prevalence was calculated using the age and sex distribution of the Swedish population in 2008. In DUS 2, the prevalence was calculated using the age and sex distribution of each specific database in 2014.

New users of cilostazol were characterised according to medical history and prior and concurrent use of medications. The number and proportion of patients were calculated for each medical condition and medication. Continuous variables were summarised by the mean, standard deviation, median, and 25th and 75th percentiles. The cumulative proportion of patients discontinuing cilostazol was calculated using survival analysis. Rates of visits were calculated as the number of visits per 100 person-years of continuous use of cilostazol, except in GePaRD where the number of diagnoses per patient-year was used (Section 9.4.5.3). Crude incidence rate ratios (RR) and 95% confidence intervals (CIs) were estimated to compare rates of visits between patients at high risk of cardiac complications (patients with history of arrhythmias, coronary heart disease, or hypotension) and patients not at high risk. All analyses were tabulated by age and sex. Age was classified in two categories: < 70 years and ≥ 70 years.

In THIN, SIDIAP, Sweden, and GePaRD, analyses were conducted using SAS versions 9.3 or 9.4 (Cary, NC: SAS Institute Inc.; 2011, 2013).[1] In EpiChron, analyses were conducted using Stata v12.0. In SIDIAP, Stata v13.1 and R 3.1.2 were also used.

9.9.2.1 Missing Values

Dose: In THIN, recorded dosage was used to calculate the daily dose of cilostazol and days of supply. Missing information on dosage (approximately 22% of prescriptions in DUS 1) was imputed from the median specific to the corresponding strength and quantity prescribed. In EpiChron, calculation of daily dose of cilostazol was restricted to patients with sufficient information (30% of prescriptions in DUS 1). In Sweden and Germany, daily dose was not available and was calculated using a twice-daily dosage based on results of descriptive analyses. In SIDIAP, information on daily dose was not available, because only the month of dispensing is recorded in the database. When information for specific variables was not available in a database (i.e., poorly controlled hypertension in EpiChron, smoking in GePaRD), the values were reported as missing. In Sweden, the smoking status was approximated by using diagnosis codes related to smoking and prescription of smoking-cessation medications.

9.9.3 Sensitivity Analyses

Sensitivity analyses were conducted to define the following activities:

- Continuous use of cilostazol by allowing a gap of 90 days from the end of days of supply of one prescription and the start date of the next prescription.
- Discontinuation of platelet aggregation inhibitors during continuous use of cilostazol, represented by lack of a subsequent prescription for a platelet aggregation inhibitor(s) recorded within 30 days and 90 days from the end of days of supply of the prior prescription for a platelet aggregation inhibitor(s).

[1] The data analysis for this paper was generated using SAS software. Copyright, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, North Carolina, USA.

- Evaluation of off-label use in GePaRD, through diagnosis codes at any time before or after the start date.

9.9.4 Amendments to the Statistical Analysis Plan

DUS 1 in GePaRD included data from two SHIs, a large one covering approximately 8 million insured members, and a smaller one covering approximately 400,000 insured members. In DUS 2, the small SHI could not contribute data to DUS 2 on time to conduct the analysis and was not included in the study. This SHI contributed less than 10% of the users in DUS 1.

9.10 Quality Control

For THIN data, upon initial receipt of the data sets by RTI-HS, they were inventoried to ensure that all expected data sets were supplied and they matched the accompanying inventory list. The data were then examined to confirm that the number of patients provided matched the number specified in the documentation. Frequencies were then performed on the variables in all of the primary data sets to ensure that the levels matched those specified in the accompanying codebooks. All analysis programming was performed in accordance with RTI Health Solutions quality-control (QC) standards. The project leader and the lead analyst determined the level of QC performed for each program. The lead analyst reviewed all logs for errors and incorporated test code throughout the program to ensure that the program was operating correctly as intended. For key programs such as cohort selection and more complex programs such as creation of drug use episodes, additional QC was performed, including having a second programmer who reviewed code for some tables or independently replicated the output of the program by following the data specification plan for other tables. QC for this final report included review of the data included by investigators not involved in the development of the report and senior review of the full study report.

Internal guidance documents at each study collaborative centre (EpiChron, IDIAP, Karolinska Institutet, BIPS) were used to guide the conduct of the study. These procedures included internal quality reviews, rules for secure and confidential data storage, methods to maintain and archive project documents, QC procedures for programming, standards for writing analysis plans, and requirements for senior scientific review. For EpiChron and SIDIAP, all programming written by one study analyst was reviewed independently by a different analyst, with oversight by a senior statistician. For Sweden, two programmers shared the work and reviewed the output from each other's programs. All key study documents, such as the analysis plan, abstraction forms, and study reports, underwent QC review, senior scientific review, and editorial review. In GePaRD, data extraction and analyses were conducted by using double-independent programming. Study results were reviewed by a statistician and by a senior epidemiologist.

10 Results

For more details on the results of DUS 1, please refer to the complete report, Cilostazol Drug Utilisation Study 1, Version 1.2, 31 March, 2015.

10.1 Results, THIN, UK

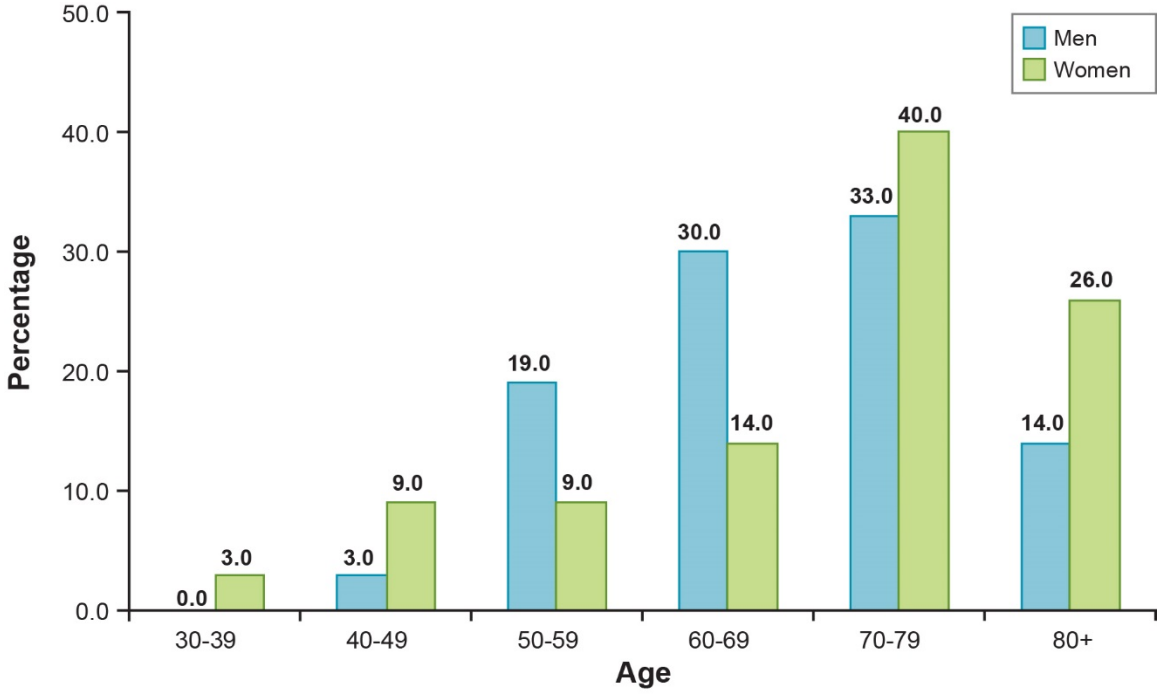
10.1.1 Participants

See file THIN3_Results_Tables.xlsx, Tables 1, 4, 25, and 32, for detailed results.

A total of 380 patients had a recorded prescription for cilostazol in 2014. Of these, 104 (27.4%) patients were new users of cilostazol and were included in the DUS 2 analysis. Only one of these cilostazol new users (1.0%) had less than 1 year of continuous enrolment in THIN.

The age and sex distribution of new users at the start date is presented in Figure 2. About 66% of users were men. The median age was 71.0 years, 69.0 years for men and 74.0 years for women (THIN, Table 31); 47.8% of men and 65.7% of women were aged 70 years or older, and 14.5% of men and 25.7% of women were aged 80 years or older (THIN3, Table 4).

Figure 2. Age and Sex Distribution of New Users of Cilostazol at the Start Date; THIN, UK



The overall and age- and sex-specific prevalence of use of cilostazol in THIN in 2014 is presented in Table 6 (THIN3, Table 25). The overall prevalence was 9.9 users per

100,000 population. Prevalence was more than the double in men (13.9 per 100,000 population) than in women (6.0 per 100,000 population) and increased by age, especially after 59 years of age. The highest prevalence was for the group aged 70 to 79 years in both men and women.

Table 6. Age- and Sex-Specific Prevalence (per 100,000 Population) of Use of Cilostazol During the DUS 2 Study Period; THIN, UK

Age in Years	Men	Women	Total
30-39	0.0	0.8	0.4
40-49	2.1	2.9	2.5
50-59	17.6	3.9	10.8
60-69	43.6	12.3	27.7
70-79	64.4	28.8	45.5
80+	41.3	20.0	28.2
Total	13.9	6.0	9.9

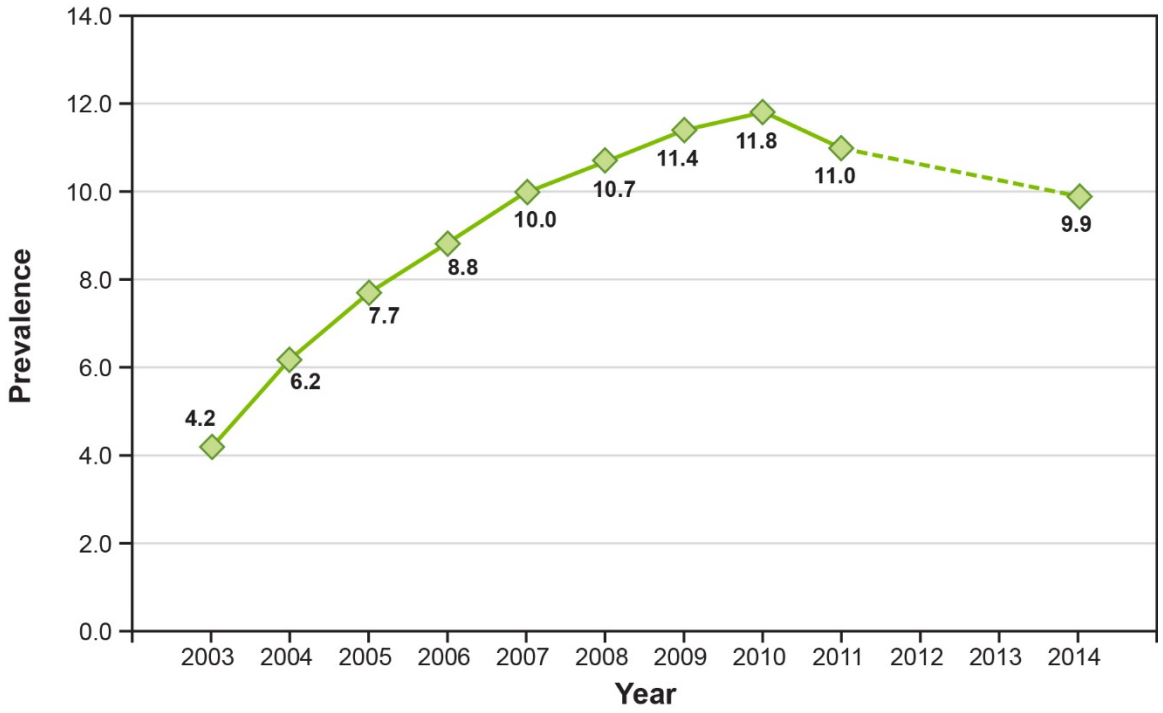
DUS = drug utilisation study; THIN = The Health Improvement Network; UK = United Kingdom.

Note: Prevalence was calculated using the age and sex distribution of the THIN population in 2014. The study period was from 1 January 2014 until 31 December 2014. There were no users of cilostazol below the age of 30 years.

In Figure 3 and Table 7, we present the prevalence of cilostazol use and the demographic characteristics of new users of cilostazol before (DUS 1) and after (DUS 2) implementation of the SmPC changes in 2013. The study period for DUS 1 was from 29 July 2002 to 14 September 2012, and the study period for DUS 2 was from 1 January 2014 to 31 December 2014. The prevalence of use in 2014, after the SmPC changes, was lower than in the 5 preceding years contributing complete annual data to the study (2007 to 2011) (Figure 3).

The proportion of men was similar in the two periods, approximately 66% of users, and new users, especially women, were slightly older in the period after the SmPC changes.

Figure 3. Annual Prevalence of Use of Cilostazol Before (2002-2012) and After (2014) the 2013 SmPC Changes; THIN, UK



DUS = drug utilisation study; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

Note: Data for the years 2002 and 2012 are not presented because use of cilostazol was not evaluated for the whole year. Data for 2013 were not evaluated because that was the year the SmPC changes were implemented. Years from 2002 to 2012 correspond to the period before the SmPC changes (DUS 1), and the year 2014 corresponds to the period after the SmPC changes (DUS 2).

Table 7. Number and Age and Sex Distribution of New Users of Cilostazol Before and After the 2013 SmPC Changes; THIN, UK

Characteristic	Before the SmPC Changes DUS 1 (N = 1,528)	After the SmPC Changes DUS 2 (N = 104)
Study period	29 Jul 2002-14 Sep 2012	1 Jan 2014-31 Dec 2014
Number of new users	1,528	104
Men (%)	65.6%	66.3%
Median age (years)		
All new users	69.0	71.0
Men	68.0	69.0
Women	71.0	74.0
Age (years)		
> 60 (%)	79.9%	78.8%
> 70 men (%)	44.4%	47.8%
> 70 women (%)	55.7%	65.7%
> 80 men (%)	12.5%	14.5%
> 80 women (%)	23.0%	25.7%
Townsend deprivation index		
1st quintile (least deprivation)	16.6%	16.3%
2nd quintile	17.9%	16.3%
3rd quintile	19.2%	19.2%
4th quintile	19.9%	25.0%
5th quintile (most deprivation)	20.0%	20.2%
Index not available	6.5%	2.9%

DUS = drug utilisation study; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

10.1.2 Descriptive Data

See Section 10.1.4, Main Results.

10.1.3 Outcome Data

Not applicable.

10.1.4 Main Results

10.1.4.1 Utilisation Patterns

See file THIN3_Results_Tables.xlsx, Tables 1 through 3, 5 through 7, 26, 29, and 30, for detailed results.

In Table 8, we present the utilisation patterns before and after implementation of the 2013 SmPC changes. The proportion of patients receiving a single prescription of

cilostazol increased from 28.6% before to 43.3% after the SmPC changes, and the proportion receiving five or more prescriptions decreased from 48.6% to 22.1%. Prescribing of the 50-mg strength increased from 25.8% of users before to 47.1% of users after the SmPC changes, and prescribing of the 100-mg strength decreased from 82.1% to 56.7% of users (THIN3, Table 1). After the SmPC changes, a higher proportion of patients received a daily dose of 100 mg (13.2% before vs. 52.9% after), and a lower proportion received a daily dose of 200 mg (85.7% before vs. 31.7% after).

Table 8. Utilisation Patterns of Cilostazol Before and After the 2013 SmPC Changes; THIN, UK

Drug Use Characteristic	Before the SmPC Changes DUS 1 (N = 1,528)	After the SmPC Changes DUS 2 (N = 104)
Total number of prescriptions	21,513	294
Mean number of prescriptions per user in study period	14.1	2.8
Total number of DDDs in study period	715,716	12,173
Mean number of DDDs per user in study period	468.4	117.0
Total number of prescriptions per user in study period		
1	28.6%	43.3%
2-4	22.8%	34.6%
5+	48.6%	22.1%
Proportion of users prescribed 50-mg strength during the study period	25.8%	47.1%
Proportion of users prescribed 100-mg strength during the study period	82.1%	56.7%
Daily dose at the start date		
100 mg	13.2%	52.9%
200 mg	85.7%	31.7%
Other	1.1%	15.4%

DDDs = defined daily doses (as defined by the World Health Organization); DUS = drug utilisation study; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

10.1.4.2 Characterisation of Users

See file THIN3_Results_Tables.xlsx, Tables 8, 9, and 24, for further detailed results.

The age and sex distribution of users of cilostazol has been described in Section 10.1.1.

The baseline comorbidity of users of cilostazol before and after the 2013 SmPC changes is presented in Table 9 (THIN3, Table 8). In both periods, the most frequent conditions (> 10% of users) were cardiovascular disease, skin disorders, renal diseases, bleeding

disorders, diabetes mellitus, asthma, malignancy, and chronic obstructive pulmonary disease (COPD). Compared with before 2013, after the SmPC changes, a similar proportion of users had a history of cardiovascular disease (91.5% before vs. 87.5% after), renal diseases (27.5% vs. 31.7%), asthma (14.1% vs. 17.3%), malignancies (12.9% vs. 16.3%), and COPD (12.7% vs. 14.4%). Prevalence of skin disorders (2.1% vs. 36.5%) and bleeding disorders (22.6% vs. 30.8%) was higher after the SmPC changes.

Table 9. Baseline Comorbidity (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; THIN, UK

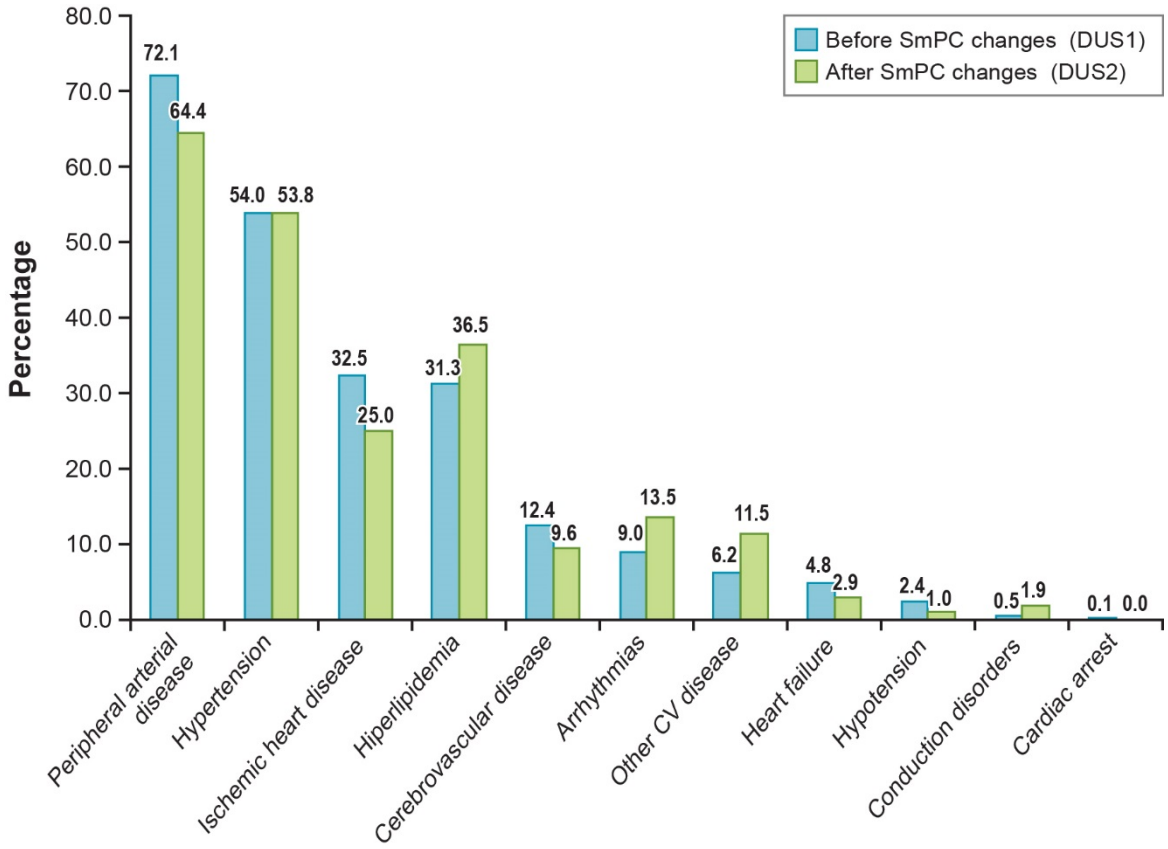
Comorbidities	Before the SmPC Changes DUS 1 (N = 1,528)	After the SmPC Changes DUS 2 (N = 104)
Cardiovascular diseases[a]	75.7	76.0
Skin disorders	26.1	36.5
Renal diseases	27.5	31.7
Bleeding disorders	22.6	30.8
Diabetes mellitus	21.3	20.2
Asthma	14.1	17.3
Malignancy	12.9	16.3
COPD	12.7	14.4
Peptic ulcer disease	8.9	2.9
Bloody dyscrasias	6.3	2.9
Rheumatoid arthritis	2.0	3.8
Liver disease	1.3	0.0
Connective tissue diseases	0.7	1.0
HIV	0.0	0.0

COPD = chronic obstructive pulmonary disease; DUS = drug utilisation study; HIV = human immunodeficiency virus; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

[a] Excluding diseases of arteries, arterioles, and capillaries.

The prevalence of cardiovascular conditions before and after the SmPC changes is presented in Figure 4. Peripheral arterial disease was the most frequent cardiovascular condition in both periods, with a lower prevalence in the period after the SmPC changes (72.1% before vs. 64.4% after). Hypertension was the second most frequent cardiovascular disease in both periods, with a similar prevalence of approximately 54% of users. After the SmPC changes, a higher proportion of users had hyperlipidemia (31.3% before vs. 36.5% after) and arrhythmias (9.0% before vs. 13.5% after), and a lower proportion had ischaemic heart disease (32.5% before vs. 25.0% after) and cerebrovascular disease (12.4% before vs. 9.6% after).

Figure 4. Baseline Cardiovascular Comorbidity (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; THIN, UK



CV = cardiovascular; DUS = drug utilisation study; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

The baseline use of comedications before and after the 2013 SmPC changes is presented in Table 10 (THIN3, Table 9). The most frequent comedications (> 10% of users) in both periods were cardiovascular drugs, antithrombotics, proton pump inhibitors, musculoskeletal system drugs, respiratory medications, antidepressants, and drugs used in diabetes. After the SmPC changes, there was a higher proportion of users of proton pump inhibitors (30.0% before vs. 49.0% after), and a lower proportion of users of musculoskeletal system drugs (24.5% before vs. 14.4% after), and drugs used in diabetes (16.7% before vs. 11.5% after). The proportion of users of cardiovascular medications, antithrombotic agents, respiratory medications, and antidepressants was similar in both periods. For antithrombotic agents, the proportion of users of platelet aggregation inhibitors decreased after the SmPC changes (67.3% before vs. 59.6% after).

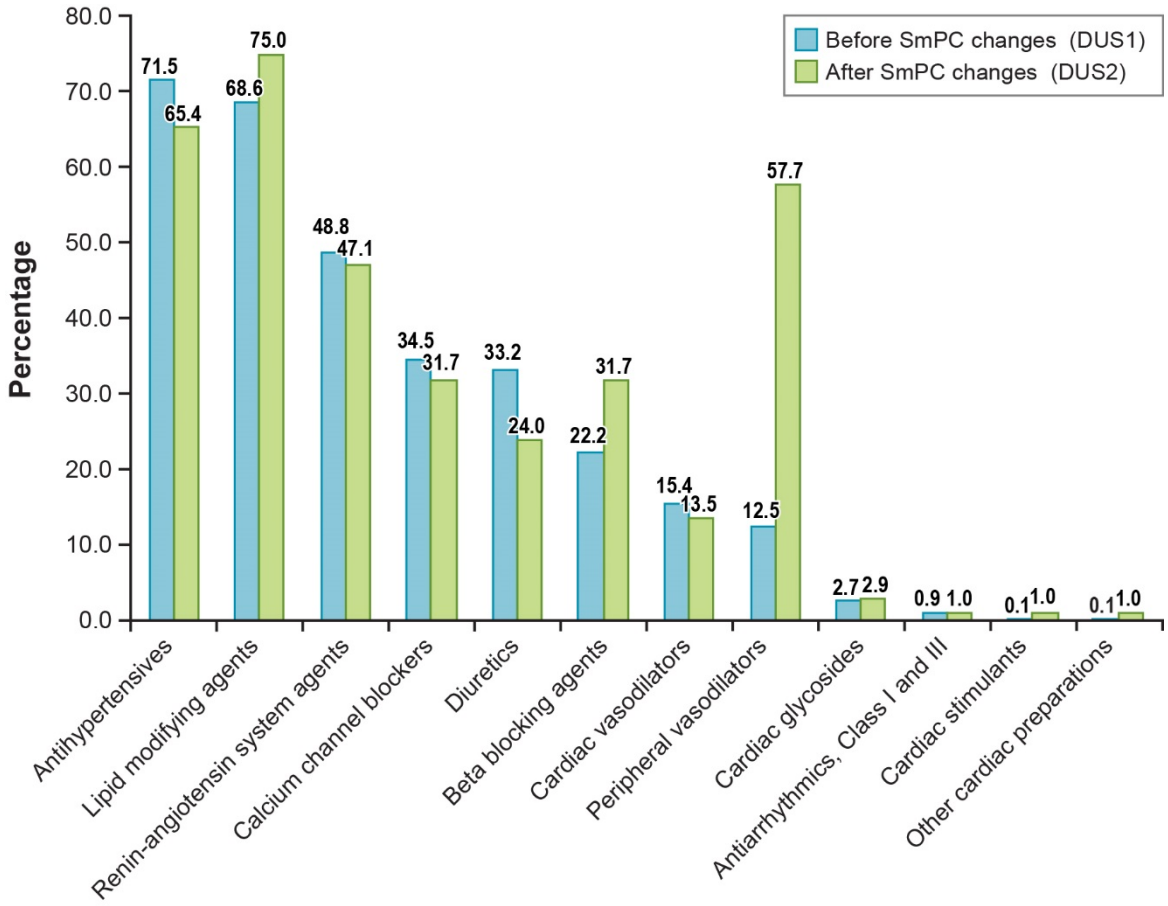
Table 10. Baseline Use of Comedications (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; THIN, UK

Comedications	Before the SmPC Changes DUS 1 (N = 1,528)	After the SmPC Changes DUS 2 (N = 104)
Cardiovascular medications	87.0	90.4
Antithrombotic agents	70.1	69.2
Platelet aggregation inhibitors	67.3	59.6
Vitamin K antagonists	3.7	8.7
Heparins	0.5	1.0
Proton pump inhibitors	30.0	49.0
Musculoskeletal system drugs	24.5	14.4
Obstructive airway disease drugs	18.7	20.2
Antidepressants	17.5	19.2
Drugs used in diabetes	16.7	11.5
Blood glucose–lowering drugs	13.8	10.6
Insulins	5.6	3.8
Peripheral vasodilators	12.5	57.7
Antinicotinics	8.7	5.8
Systemic corticosteroids	7.9	8.7
Iron preparations	5.8	3.8
Hormone replacement therapy	2.9	4.8
Antineoplastic agents	0.9	2.9
Immunosuppressants	0.7	0.0
Antivirals	0.5	1.0

DUS = drug utilisation study; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

The baseline use of cardiovascular medications before and after the SmPC changes is presented in Figure 5. Antihypertensives and lipid-modifying agents were the most frequent baseline comedications before and after the 2013 SmPC changes. Other frequent cardiovascular medications were renin-angiotensin system agents, calcium channel blockers, diuretics, and beta-blocking agents. After the SmPC changes, the use of lipid-modifying agents (68.6% before vs. 75.0% after) and beta-blocking agents (22.2% before vs. 31.7% after) increased, and the use of antihypertensives (71.5% before vs. 65.4% after) and diuretics (33.2% before vs. 24.0% after) decreased. An increase in the use of peripheral vasodilators after the SmPC changes was due to the use of naftidrofuryl (ATC code C04AX21), which was approved for intermittent claudication in the UK in May 2011.

Figure 5. Baseline Use of Cardiovascular Comedications (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; THIN, UK



DUS = drug utilisation study; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

10.1.4.3 Concurrent Use of Potentially Interacting Medications

See file THIN3_Results_Tables.xlsx, Tables 10 through 13, and 27 for further detailed results.

The concurrent use of potentially interacting comedications before and after the 2013 SmPC changes is presented in Table 11 (THIN3, Table 13). Most users were concurrently treated with potentially interacting medications in both periods, 91.6% before the SmPC changes and 91.3% after the SmPC changes. In both periods, the concurrent use of interacting medications was higher for drugs interacting with the CYP3A4 enzyme than for those interacting with the CYP2C19 enzyme.

The concurrent use of CYP3A4 and CYP2C19 potent inhibitors at the start date was higher after the SmPC changes (11.6% before vs. 15.4% after). Concurrent use at the start date and/or continuous use during follow-up was lower after the SmPC changes (22.3% before vs. 17.3% after).

Table 11. Concurrent Use of Potentially Interacting Medications (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; THIN, UK

Interaction Medications	Before the SmPC Changes DUS 1 (N = 1,528)	After the SmPC Changes DUS 2 (N = 104)
Any interaction medication	91.6	91.3
Drugs interacting with CYP2C19	55.3	58.7
Substrates	54.6	57.7
Inhibitors	36.9	43.3
Drugs interacting with CYP3A4	85.3	83.7
Substrates	84.6	83.7
Inhibitors	20.5	12.5
Inducers	3.6	1.9
Potent inhibitors	22.3	17.3
CYP2C19 potent inhibitors	16.0	10.6
CYP3A4 potent inhibitors	8.7	7.7

DUS = drug utilisation study; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

Note: Potent CYP3A4 or CYP2C19 inhibitors were lansoprazole, fluvoxamine, nefazodone, ticlopidine, clarithromycin, troleandomycin, indinavir, ritonavir, nelfinavir, mibefradil, ketoconazole, and itraconazole.

The most frequently prescribed medications interacting with the CYP3A4 enzyme before and after the SmPC changes were simvastatin, atorvastatin, amlodipine, and quinine (Table 12), and the most frequently prescribed medications interacting with the CYP2C19 enzyme were omeprazole, clopidogrel, lansoprazole, and amitriptyline (Table 13). After the SmPC changes, there was a higher proportion of users of omeprazole (22.4% before vs. 31.7% after) and amitriptyline (9.9% before vs. 15.4% after), and a lower proportion of users of clopidogrel (18.2% before vs. 11.5% after) and lansoprazole (16.0% before vs. 10.6% after).

Table 12. Concurrent Use of Cilostazol and Medications Interacting With the CYP3A4 Enzyme (Proportion), Before and After the 2013 SmPC Changes; THIN, UK

Interaction Medication	Before the SmPC Changes DUS 1 (N = 1,528)	After the SmPC Changes DUS 2 (N = 104)
Simvastatin	44.0	42.3
Atorvastatin	29.3	26.0
Amlodipine	22.2	13.5
Quinine	11.2	9.6
Clarithromycin	8.4	7.7
Diazepam	7.7	6.7
Nifedipine	6.5	5.8
Erythromycin	6.2	1.9

Interaction Medication	Before the SmPC Changes DUS 1 (N = 1,528)	After the SmPC Changes DUS 2 (N = 104)
Diltiazem	6.1	1.9
Felodipine	4.5	5.8
Sildenafil	2.8	1.9
Chlorpheniramine	2.4	1.9
Amiodarone	1.8	1.0
Pioglitazone	1.6	0.0
Verapamil	1.4	0.0
Carbamazepine	1.0	1.0
Phenytoin	0.9	1.0
Cimetidine	0.8	0.0
Midazolam	0.6	0.0
Trazodone	0.4	0.0
Haloperidol	0.3	0.0
Tamoxifen	0.3	0.0
Itraconazole	0.3	0.0
Rifampicin	0.2	0.0
Buspirone	0.1	1.0
Cyclosporine	0.1	0.0
Methadone	0.1	0.0

DUS = drug utilisation study; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

Table 13. Concurrent Use of Cilostazol and Medications Interacting With the CYP2C19 Enzyme (Proportion), Before and After the 2013 SmPC Changes; THIN, UK

Interaction Medication	Before the SmPC Changes DUS 1 (N = 1,528)	After the SmPC Changes DUS 2 (N = 104)
Omeprazole	22.4	31.7
Clopidogrel	18.2	11.5
Lansoprazole	16.0	10.6
Amitriptyline	9.9	15.4
Diazepam	7.7	6.7
Pantoprazole	6.2	1.9
Fluoxetine	3.6	1.9
Rabeprazole	2.6	1.0
Phenytoin	0.9	1.0
Clomipramine	0.3	0.0
Cyclophosphamide	0.1	0.0

DUS = drug utilisation study; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

The proportion of users concurrently treated with four or more interacting medications decreased from 21.1% before to 11.5% after the 2013 SmPC changes. The proportion of users treated with three interacting medications was 18.2% before and 17.3% after; two interacting medications, 27.7% and 37.5%; and a single interacting medication, 24.7% and 25.0% (THIN3, Table 27).

10.1.4.4 Concurrent Use and Discontinuation of Antithrombotic Agents

See file THIN3_Results_Tables.xlsx, Tables 14, 15, and 16, for further detailed results.

The proportion of users concurrently treated with antithrombotic agents decreased from 79.2% of users to 62.5% of users after the 2013 SmPC changes. For platelet aggregation inhibitors, the decrease was from 76.4% before to 54.8% after the SmPC changes. The most frequently prescribed platelet aggregation inhibitors were acetylsalicylic acid (66.6% before vs. 48.1% after) and clopidogrel (16.7% before vs. 8.7% after) (THIN3, Table 15).

Discontinuation of platelet aggregation inhibitors in the 60 days after the start of cilostazol decreased from 16.3% of cilostazol users before to 6.7% after the SmPC changes. In the sensitivity analysis, when the period to assess discontinuation of platelet aggregation inhibitors was reduced to 30 days, the discontinuation of platelet aggregation inhibitors decreased from 28.9% of cilostazol users before to 9.1% after the SmPC changes. When the period of assessment was extended to 90 days, the discontinuation of platelet aggregation inhibitors decreased from 12.8% of cilostazol users before to 3.3% after the SmPC changes (THIN3, Table 16).

10.1.4.5 Evaluation of Changes to the Summary of Product Characteristics

See file THIN3_Results_Tables.xlsx, Tables 17 through 20, for further detailed results.

In this section, we present the frequency of conditions included in the new cilostazol SmPC before and after implementation of the 2013 changes in the SmPC. Conditions evaluated were smoking status at the start date, monitoring of patients after 3 months of initiating treatment, discontinuation of cilostazol, old and new contraindications, monitoring of patients at high risk of cardiovascular events, and reduction of daily dose from 200 mg to 100 mg in patients concurrently treated with interacting medications.

Smoking Status at the Start Date

The proportion of users that were current smokers at the start date increased from 30.4% before to 37.5% after the SmPC changes (THIN3, Table 17A).

Monitoring of Patients After 3 Months to Evaluate Inadequate Effect of Cilostazol

For both periods, before and after the 2013 SmPC changes, visits to the GP and to specialists were evaluated for the period from 2 months to 4 months after the start date among patients who continued using cilostazol within 3 months after the start date.

Visits were assessed by (1) manual review of patient profiles and free text (random sample in DUS 1, and all eligible patients in DUS 2), and (2) examination of Read codes among all eligible patients. The clinical review of patient profiles and free text provides the most comprehensive information as it includes notes and comments that the GPs enter into the electronic medical records.

The evaluation of visits between 2 months and 4 months after the start date, before and after the 2013 SmPC changes, is presented in Table 14 (THIN3, Tables 17B and 17C). After the SmPC changes, 32 patients (30.8%) were treated with cilostazol 3 months after the start date. Results from the clinical review of patient profiles and free text for these patients revealed that the proportion of patients with a GP or specialist visit increased from 80.9% to 96.2%, and the proportion of patients with a visit related to intermittent claudication or peripheral arterial disease increased from 49.6% to 69.2%. Results from the analysis of Read codes were similar in both periods.

Table 14. Evaluation of Visits Between 2 Months and 4 Months After the Start Date to Evaluate Inadequate Effect of Cilostazol, Before and After the 2013 SmPC Changes; THIN, UK

	Clinical Review of Patient Profiles and Free Text		Analysis of Read Codes	
	Before the SmPC Changes DUS 1 (n = 115)	After the SmPC Changes DUS 2 (n = 26)	Before the SmPC Changes DUS 1 (n = 800)	After the SmPC Changes DUS 2 (n = 32)
Type of Visit	**%**	**%**	**%**	**%**
GP only	52.2	69.2	62.6	65.6
Related to IC/PAD	20.9	42.3	6.6	3.1
Unrelated/unknown	31.3	26.9	56.0	62.5
Specialist[a]	28.7	26.9	11.9	9.4
Vascular clinic	19.1	23.1	6.0	6.3
Diabetic clinic	7.0	3.8	4.6	3.1
Cardiology clinic	4.3	0.0	1.8	0.0
Patients without visits	19.1	3.8	25.5	25.0
Total GP or specialist[a]	80.9	96.2	74.5	75.0
Total GP related to IC/PAD or specialist	49.6	69.2	18.5	12.5

DUS = drug utilisation study; GP = general practitioner; IC = intermittent claudication; PAD = peripheral arterial disease; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

[a] Patients could have visits to more than one specialist and could also have one or more visits to the GP.

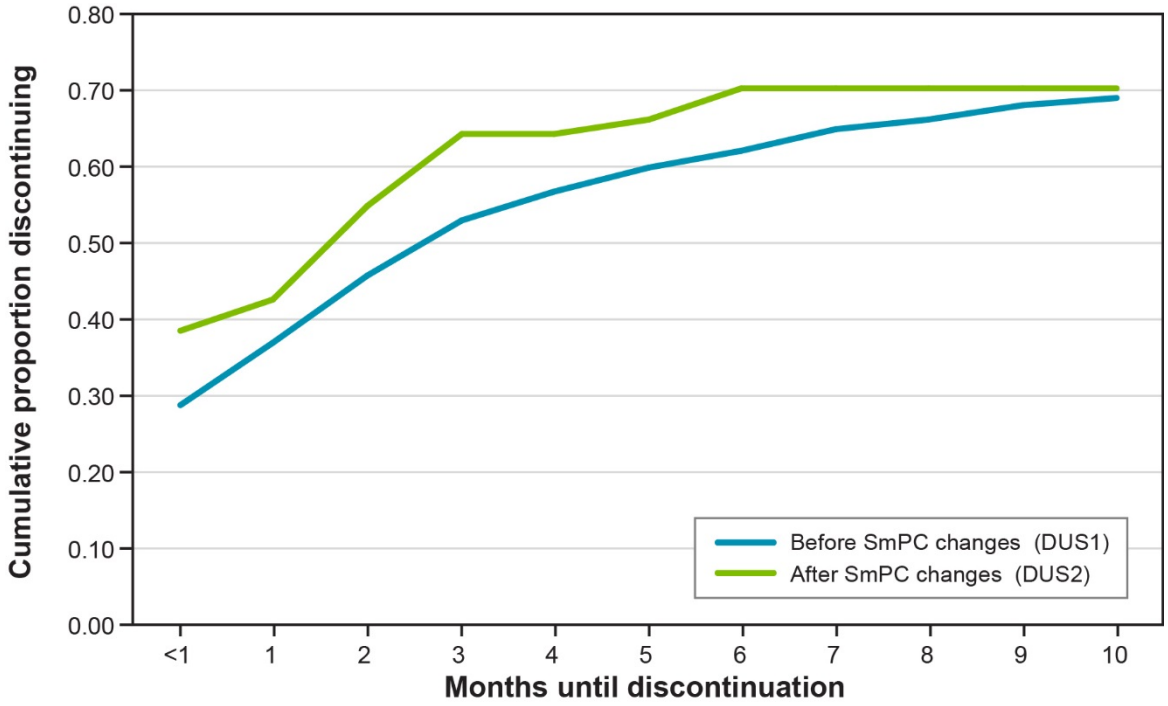
In a sensitivity analysis evaluating the period between 1 month and 6 months after the start date by reviewing patient profiles and free text, the proportion of patients with a GP or specialist visit increased from 96.5% before to 100% after the SmPC changes, and

the proportion of patients with a visit related to intermittent claudication or peripheral arterial disease increased from 61.7% to 80.8% (THIN3, Table 17b).

Discontinuation of Cilostazol

Results from the survival analysis of the cumulative proportion of patients discontinuing cilostazol, by month, before and after the 2013 SmPC changes are presented in Figure 6 (THIN3, Table 17A).

Figure 6. Survival Analysis of Cilostazol Discontinuation Among New Users of Cilostazol Before and After the 2013 SmPC Changes, by Month; THIN, UK



DUS = drug utilisation study; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

A similar proportion of patients discontinued cilostazol in the first month of treatment: 37.0% before the SmPC changes and 38.5% after the SmPC changes. The proportion discontinuing in the first 3 months of treatment increased from 52.9% before to 64.4% after the SmPC changes, and the proportion discontinuing in the first 6 months of treatment increased from 62.2% before to 70.3% after the SmPC changes. The proportion discontinuing in the first 12 months of treatment was similar before (71.3%) and after (70.3%) the SmPC changes.

Contraindications

In Table 15, we present the number and proportion of users of cilostazol who had contraindications at the start of cilostazol treatment before and after the SmPC changes. Contraindications evaluated were those included in the labelling before the SmPC revision in 2013 (old contraindications) and those added in the labelling in the SmPC 2013 revision (new contraindications) (THIN Tables 17A, 20, 28).

The proportion of patients with old contraindications was similar before (10.0%) and after (8.7%) the SmPC changes. The proportion of users with new contraindications decreased from 10.7% before to 3.8% after the SmPC changes. Cardiovascular contraindications decreased from 1.5% before to 1.0% after the SmPC changes. Concurrent use of cilostazol and two or more platelet aggregation inhibitors decreased from 9.8% to 2.9%. Overall, the proportion of patients with contraindications (old and/or new) decreased from 19.6% before to 11.5% after the SmPC changes.

Table 15. Contraindications Before and After the 2013 SmPC Changes; THIN, UK

	Before the SmPC Changes DUS 1 (N = 1,528)		After the SmPC Changes DUS 2 (N = 104)	
Contraindication	**Number of Patients**	**Proportion**	**Number of Patients**	**Proportion**
Old contraindications (before 2013 SmPC revision)	**153**	**10.0**	**9**	**8.7**
Renal failure	37	2.4	5	4.8
Liver disease	20	1.3	0	0.0
Heart failure	73	4.8	3	2.9
Conditions predisposing to bleeding	27	1.8	1	1.0
Active peptic ulcer	1	0.1	0	0.0
Recent cerebral haemorrhage	0	0.0	0	0.0
Proliferative diabetic retinopathy	10	0.7	0	0.0
Poorly controlled hypertension	16	1.0	1	1.0
Arrhythmias	10	0.7	0	0.0
Ventricular tachycardia	2	0.1	0	0.0
Ventricular fibrillation or multifocal ventricular ectopics	8	0.5	0	0.0
Prolongation of the QT interval	0	0.0	0	0.0
New contraindications (2013 SmPC revision)[a]	**164**	**10.7**	**4**	**3.8**
Cardiovascular diagnosis within 6 months before the start date	23	1.5	1	1.0
Myocardial infarction	11	0.7	1	1.0
Unstable angina	4	0.3	0	0.0
Coronary intervention	11	0.7	0	0.0
Concurrent use of cilostazol with two or more platelet aggregation inhibitors				
At the start date	80	5.2	3	2.9
At the start date and/or during continuous use of cilostazol	149	9.8	3	2.9
Any contraindication (old and new)	**299**	**19.6**	**12**	**11.5**

DUS = drug utilisation study; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

[a] New contraindications were added to labelling in addition to the old contraindications.

Monitoring of Patients at Increased Risk of Serious Cardiac Events

Rates of visits (to a physician) during continuous use of cilostazol were compared between users at increased risk of serious cardiac events and users not at increased risk. Increased risk was defined as a history of arrhythmias, coronary heart disease, or hypotension at any time before the start date.

Among the 104 new users of cilostazol included in DUS 2 (after the SmPC changes), 34 patients were at increased risk of serious cardiovascular events, and 70 patients were not at increased risk.

The rate of visits per 100 person-years in patients at increased risk decreased from 1,457 (95% CI, 1,430-1,485) before to 1,897 (95% CI, 1,567-2,275) after the SmPC changes. The rate in patients not at increased risk increased from 1,354 (95% CI, 1,335-1,373) before to 2,149 (95% CI, 1,933-2,381) after the SmPC changes. The RR comparing rates of visits between patients at increased risk and patients not at increased risk was 1.08 (95% CI, 1.05-1.10) in the period before the SmPC changes and 0.88 (95% CI, 0.71-1.09) in the period after the SmPC changes.

Reduction of Daily Dose in Patients Receiving Potentially Interacting Medications

The proportion of patients treated with interacting medications and cilostazol 200 mg daily at the start date decreased from 71.2% before to 27.9% after the SmPC changes. During follow-up, 114 (7.5%) patients before and no patients after the SmPC changes were concurrently treated with interacting medications and a daily dose of 200 mg (THIN Table 18). Before the SmPC changes, the daily dose of 200 mg was not reduced in any of the 114 patients concurrently treated with interacting medications.

For concurrent use of CYP3A4 or CYP2C19 potent inhibitors, at the start date 9.9% of patients before the SmPC changes were concurrently treated with a daily dose of cilostazol 200 mg. This proportion decreased to 5.8% after the SmPC changes. During follow-up, 148 (9.7%) patients before and no patients after the SmPC changes were concurrently treated with CYP3A4 or CYP2C19 potent inhibitors and a cilostazol daily dose of 200 mg. Before the SmPC changes, the daily dose of 200 mg was not reduced in any of the 148 patients concurrently treated with potent inhibitors.

Summary of the Evaluation of Changes to the Summary of Product Characteristics

A summary of the evaluation of the 2013 the SmPC changes is presented in Table 16. Compared to the period before the SmPC changes, the period after the SmPC changes was characterised by a higher prevalence of smoking at the start date; an increase in the monitoring and early discontinuation of patients at the beginning of treatment; a decrease in the prevalence of new cardiovascular contraindications and concurrent use of cilostazol and two or more platelet aggregation inhibitors; an increase in the monitoring of patients at high risk of severe cardiovascular events; and a decrease in the concurrent

use of a high daily dose of cilostazol and interacting medications, including CYP3A4 or CYP2C19 potent inhibitors.

Table 16. Overall Assessment of Variables Affected by the 2013 SmPC, Before and After the SmPC Changes; THIN, UK

2013 Changes to the Summary of Product Characteristics	Study Variable	Before the SmPC Changes DUS 1 (N = 1,528) n (%) or Rate[a] (95% CI)	After the SmPC Changes DUS 2 (N = 104) n (%) or Rate[a] (95% CI)
Indication			
Second-line use after lifestyle modifications, including smoking cessation and (supervised) exercise programmes, failed to sufficiently improve symptoms	Current smoking at the start date	464 (30.4)	39 (37.5)
Physician reassessment of patients after 3 months of treatment with a view to discontinuing cilostazol if an inadequate effect is observed	▪ Visit to GP or specialist between 2 and 4 months after the start date	93 (80.9)[a]	25 (96.2)[b]
	▪ Visit related to intermittent claudication	57 (49.6)[a]	18 (69.2)[b]
	▪ Discontinuation before 3 months of treatment (cumulative proportion discontinuing)[c]	52.9	64.4
Contraindications			
Unstable angina pectoris, myocardial infarction within the last 6 months, or a coronary intervention in the last 6 months	As described in labelling	23 (1.5)	1 (1.0)
Concomitant treatment with two or more additional platelet aggregation inhibitors (e.g., aspirin, clopidogrel) at the start date and/or during follow-up	As described in labelling	149 (9.8)	3 (3.8)
Warnings and precautions			
Close monitoring of patients at increased risk for serious cardiac adverse events as a result of increased heart rate, e.g., patients with stable coronary disease or a history of tachyarrhythmias	Rate of visits to GP or specialist per 100 person-years		
	▪ No increased risk	1,354 (1,335-1,373)	2,149 (1,933-2,381)
	▪ Increased risk	1,457 (1,430-1,485)	1,897 (1,567-2,275)
	▪ RR increased/no increased risk	1.08 (1.05-1.10)	0.88 (0.71-1.09)

2013 Changes to the Summary of Product Characteristics	Study Variable	Before the SmPC Changes DUS 1 (N = 1,528) n (%) or Rate[a] (95% CI)	After the SmPC Changes DUS 2 (N = 104) n (%) or Rate[a] (95% CI)
Posology			
Reduction of daily dose to 100 mg in patients receiving medicines interacting with CYP3A4 or CYP2C19 enzymes			
Any interacting medication	Concurrent use of cilostazol 200 mg per day and interacting medications	1,202 (78.7)	29 (27.9)
	▪ At the start date	1,088 (71.2)	29 (27.9)
	▪ During follow-up	114 (7.5)	0 (0.0)
	Dose reduction after start of an interacting medication during follow-up	0 of 114 (0.0)	NA (0 patients with a daily dose of 200 mg during follow-up)
CYP3A4 or CYP2C19 potent inhibitors[d]	Concurrent use of cilostazol 200 mg per day and potent inhibitors	299 (19.6)	6 (5.8)
	▪ At the start date	151 (9.9)	6 (5.8)
	▪ During follow-up	148 (9.7)	0 (0.0)
	Dose reduction after start of a potent inhibitor during follow-up	0 of 148 (0.0)	NA (0 patients with a daily dose of 200 mg during follow-up)

CI = confidence interval; DUS = drug utilisation study; GP = general practitioner; NA = not applicable; RR = rate ratio; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

[a] Based on the review of patient profiles and free text of a random sample of 115 patients treated with cilostazol 3 months after the start date.

[b] Based on the review of patient profiles and free text of all patients in DUS 2 treated with cilostazol 3 months after the start date (N = 114).

[c] Cumulative proportion of patients discontinuing calculated using survival analysis.

[d] Potent CYP3A4 or CYP2C19 inhibitors: lansoprazole, fluvoxamine, nefazodone, ticlopidine, clarithromycin, troleandomycin, indinavir, ritonavir, nelfinavir, mibefradil, ketoconazole, and itraconazole.

10.1.4.6 Indication and Off-Label Use

See file THIN3_Results_Tables.xlsx, Table 21, for further detailed results.

The potential indication and off-label use of cilostazol was evaluated through the clinical review of patient profiles in both periods before and after the SmPC changes. In DUS 1, the review was conducted in a random sample of 197 patients (three patients from an initial sample of 200 patients did not meet the study eligibility criteria and were excluded). In DUS 2, the review of patient profiles and free text was conducted for all the 104 patients included in the study.

Results from the review are presented in Table 17. Potential off-label prescribing of cilostazol increased from 5.6% of users before to 9.6% after the SmPC changes. The proportion of users with a specific diagnosis of intermittent claudication before initiating cilostazol was lower after the SmPC changes (51.0%) than before the SmPC changes (64.5%). Leg pain was the most frequent potential off-label diagnosis in both periods.

Table 17. Indication and Potential Off-Label Prescribing of Cilostazol—Review of Patient Profiles and Free Text, Before and After the 2013 SmPC Changes; THIN, UK

	Before the SmPC Changes DUS 1 (N = 197)		After the SmPC Changes DUS 2 (N = 104)	
Category and Diagnosis	**Number of Users**	**Proportion**	**Number of Users**	**Proportion**
Patient profiles reviewed	197	100.0	104	100.0
On-label diagnosis[a]	184	93.4	87	83.7
Intermittent claudication[b]	127	64.5	53	51.0
Potential off-label diagnosis	11[c]	5.6	10	9.6
Leg/arm pain	7	3.6	8	7.7
Peripheral neuropathy	2	1.0	0	0.0
Cerebrovascular accident	2	1.0	1	1.0
Ischaemic heart disease	1	0.5	1	1.0
Other diagnoses or no diagnosis recorded	2	1.0	7	6.7

DUS = drug utilisation study; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

[a] Diagnosis of intermittent claudication and/or peripheral arterial disease before the start date.

[b] Diagnosis of intermittent claudication with or without a diagnosis of peripheral arterial disease.

[c] One patient had two potential off-label diagnoses.

10.1.4.7 Hospitalisations

See file THIN3_Results_Tables.xlsx, Table 22, for detailed results.

The proportion of patients who had at least one hospitalisation during the period of continuous use of cilostazol decreased from 25.3% before to 10.6% after the SmPC changes.

10.2 Results, EpiChron, Aragón, Spain

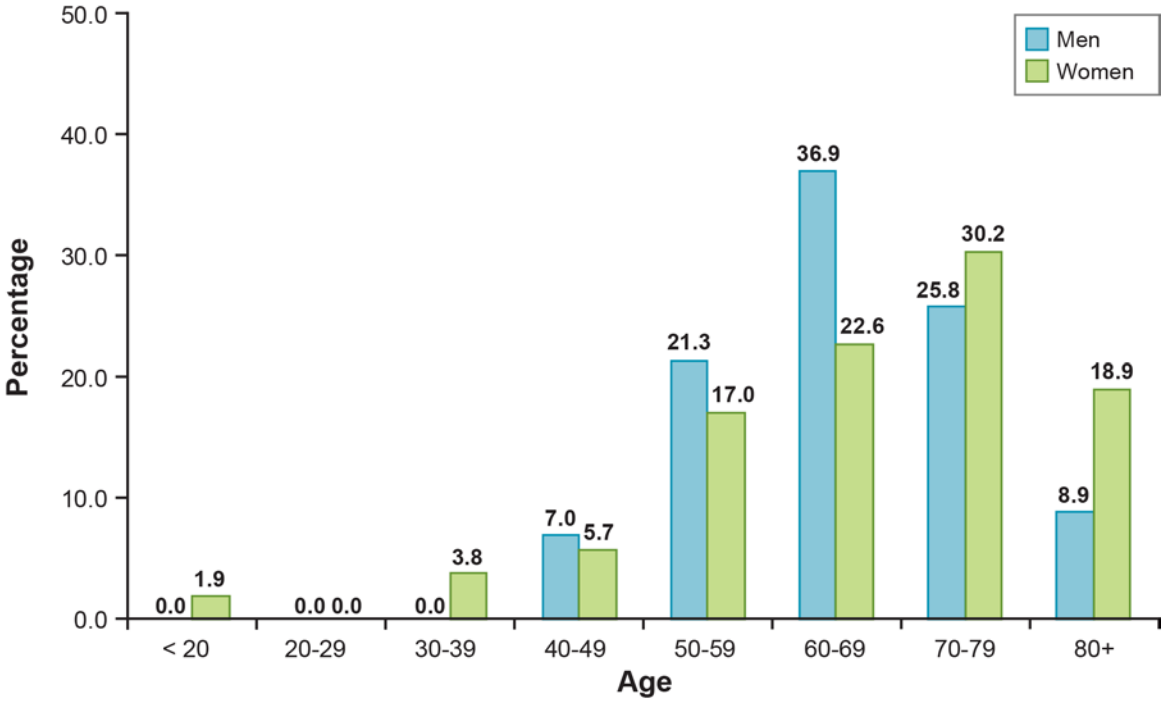
10.2.1 Participants

See file EpiChron_Results_Tables.xlsx, Tables 1, 4, 25, and 31, for detailed results.

A total of 1,670 patients had a recorded prescription for cilostazol in 2014; of these, 367 (22.0%) patients were new users of cilostazol and were included in the DUS 2 analysis. Only two of these cilostazol new users (0.5%) had less than 1 year of continuous enrolment in the EpiChron Cohort.

The age and sex distribution of new users at the start date is presented in Figure 7. About 86% of new users were men. The median age was 66.3 years, 65.9 years for men and 69.7 years for women (EpiChron, Table 31); 71.7% of users were aged 60 or older, 34.7% of men and 49.1% of women were aged 70 years or older, and 8.9% of men and 18.9% of women were aged 80 years or older (EpiChron, Table 4).

Figure 7. Age and Sex Distribution of New Users of Cilostazol at the Start Date; EpiChron, Aragón, Spain



The prevalence of use of cilostazol (new and prevalent users) in EpiChron in 2014 is presented in Table 18 (EpiChron, Table 25). The overall prevalence was 161.5 users per 100,000 population. Prevalence was higher in men (291.4 per 100,000 population) than in women (38.1 per 100,000 population) and increased by age, especially after 49 years of age. The highest prevalence was for the group aged 70-79 years in men and for the group aged 80+ years in women.

Table 18. Age- and Sex-Specific Prevalence (per 100,000 Population) of Use of Cilostazol During the DUS 2 Study Period; EpiChron, Aragón, Spain

Age in Years	Men	Women	Total
<30	0.0	1.5	0.8
30-39	1.0	8.4	4.6
40-49	46.3	4.9	26.1
50-59	259.7	32.9	147.3
60-69	786.1	61.6	412.4
70-79	922.3	95.3	468.5
80+	738.8	114.5	348.8
Total	291.4	38.1	161.5

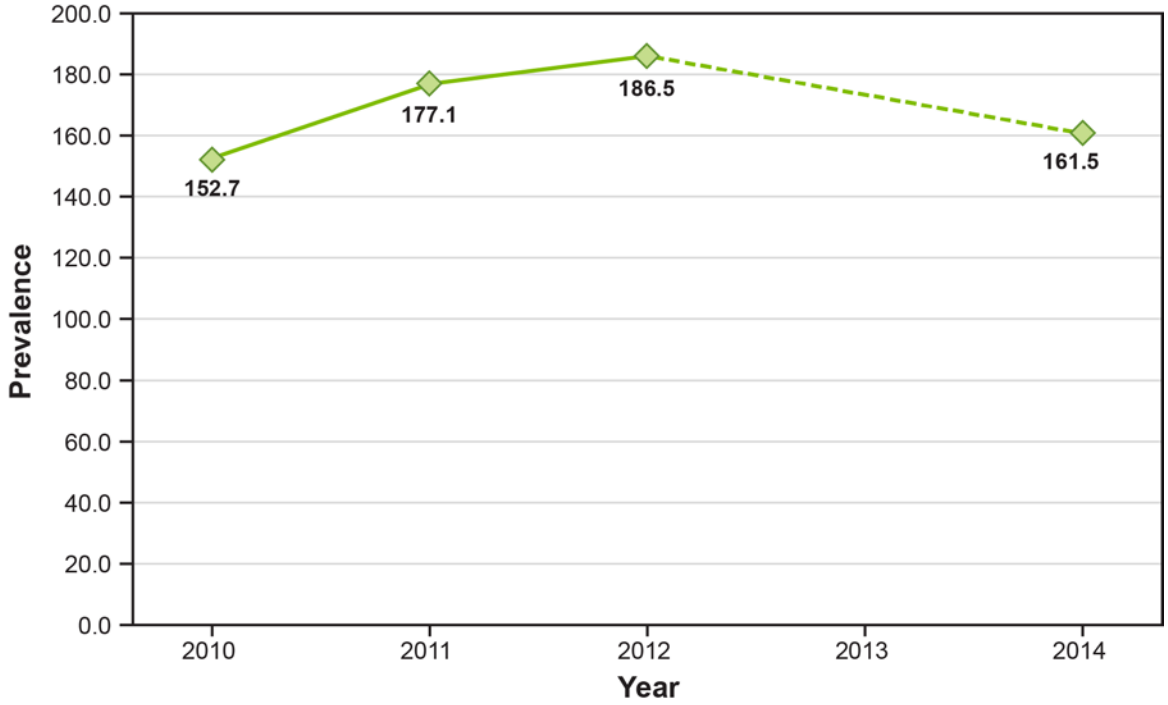
DUS = drug utilisation study.

Note: Prevalence was calculated using the age and sex distribution of the population in Aragón in 2014. The study period was from 1 January 2014 until 31 December 2014.

In Figure 8 and Table 19, we present the prevalence of cilostazol use and the demographic characteristics of new users of cilostazol before (DUS 1) and after (DUS 2) implementation of the SmPC changes in 2013. The study period for DUS 1 was from 1 June 2009 to 31 December 2012, and the study period for DUS 2 was from 1 January 2014 to 31 December 2014. The prevalence of use in 2014, after the SmPC changes, was lower than in the 2 preceding years contributing complete annual data to the study (2011 to 2012) (Figure 8).

In both periods, the proportion of men was higher, and new users, especially women, were slightly older.

Figure 8. Annual Prevalence of Use of Cilostazol Before (2010-2012) and After (2014) the 2013 SmPC Changes; EpiChron, Aragón, Spain



DUS = drug utilisation study; SmPC = summary of product characteristics.

Note: Data for the year 2009 are not presented because use of cilostazol was not evaluated for the whole year. Data for 2013 were not evaluated because that was the year the SmPC changes were implemented. Years from 2010 to 2012 correspond to the period before the SmPC changes (DUS 1), and the year 2014 corresponds to the period after the SmPC changes (DUS 2).

Table 19. Number and Age and Sex Distribution of New Users of Cilostazol Before and After the 2013 SmPC Changes; EpiChron, Aragón, Spain

Characteristic	Before the SmPC Changes DUS 1 (N = 4,024)	After the SmPC Changes DUS 2 (N = 367)
Study period	1 Jun 2009-31 Dec 2012	1 Jan 2014-31 Dec 2014
Number of new users	4,024	367
Men (%)	72.2%	85.6%
Median age (years)		
All new users	70.1	66.3
Men	69.0	65.9
Women	73.9	69.7
Age (years)		
> 60 (%)	77.5%	71.7%
> 70 men (%)	46.9%	34.7%
> 70 women (%)	58.5%	49.1%
> 80 men (%)	16.5%	8.9%
> 80 women (%)	25.7%	18.9%

DUS = drug utilisation study; SmPC = summary of product characteristics.

10.2.2 Descriptive Data

See Section 10.1.4, Main Results.

10.2.3 Outcome Data

Not applicable.

10.2.4 Main Results

10.2.4.1 Utilisation Patterns

See file EpiChron_Results_Tables.xlsx, Tables 1 through 3, 5 through 7, 26, 29, and 30, for detailed results.

In Table 20, we present the utilisation patterns before and after implementation of the 2013 SmPC changes. The proportion of patients dispensed a single dispensing of cilostazol increased from 31.1% before to 37.1% after the SmPC changes, and the proportion receiving five or more dispensings decreased from 48.5% to 30.0%. The cilostazol formulation strength of 50 mg became available in Spain only after the SmPC changes in 2013; therefore, only the strength of 100 mg was included in DUS 1. After the SmPC changes, 33.5% of patients received a strength of 50 mg and 73.8% a strength of 100 mg, during the study period.

In DUS 2, information required to calculate the prescribed daily dose at the start date was available for 28 patients (7.6%) in DUS 2. After the SmPC changes, a higher proportion of patients received a daily dose of 100 mg (21.6% before vs. 92.9% after), and a lower proportion received a daily dose of 200 mg (77.3% before vs. 7.1% after).

Table 20. Utilisation Patterns of Cilostazol Before and After the 2013 SmPC Changes; EpiChron, Aragón, Spain

Drug Use Characteristic	Before the SmPC Changes DUS 1 (N = 4,024)	After the SmPC Changes DUS 2 (N = 367)
Total number of prescriptions	35,719	1,372
Mean number of prescriptions per user in study period	8.9	3.7
Total number of DDDs in study period	1,133,944	33,208
Mean number of DDDs per user in study period	281.8	90.5
Total number of prescriptions per user in study period		
1	31.1%	35.2%
2-4	20.4%	34.9%
5+	48.5%	30.0%

Drug Use Characteristic	Before the SmPC Changes DUS 1 (N = 4,024)	After the SmPC Changes DUS 2 (N = 367)
Proportion of users dispensed 50-mg strength during the study period	NA	33.5%
Proportion of users dispensed 100-mg strength during the study period	100%	73.8%
Daily dose at the start date[a]		
100 mg	21.6%	92.9%
200 mg	77.3%	7.1%
Other	0.9%	0.0%

DDDs = defined daily doses (as defined by the World Health Organization); DUS = drug utilisation study; NA = not applicable; SmPC = summary of product characteristics.

[a] Information on daily dose was available for 1,249 patients (30.0%) in DUS 1 and for 28 patients (7.6%) in DUS 2.

10.2.4.2 Characterisation of Users

See file EpiChron_Results_Tables.xlsx, Tables 8, 9, and 24, for further detailed results.

The age and sex distribution of users of cilostazol has been described in Section 10.1.1.

The baseline comorbidity of users of cilostazol was higher before than after the 2013 SmPC changes (EpiChron, Table 8). In both periods, the most frequent conditions (> 10% of users) were cardiovascular disease, diabetes mellitus, COPD, and skin disorders. After the SmPC changes, a lower proportion of users had a history of cardiovascular disease (74.5% before vs. 57.8% after), diabetes mellitus (29.9% before vs. 23.4% after), COPD (17.3% before vs. 13.1% after), skin disorders (15.9% before vs. 9.8% after), and renal diseases (12.8% before vs. 5.2% after) (Table 21).

Table 21. Baseline Comorbidity (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; EpiChron, Aragón, Spain

Comorbidities	Before the SmPC changes DUS 1 (N = 4,024)	After the SmPC changes DUS 2 (N = 367)
Cardiovascular diseases[a]	74.5%	57.8%
Diabetes mellitus	29.9%	23.4%
COPD	17.3%	13.1%
Skin disorders	15.9%	9.8%
Renal diseases	12.8%	5.2%
Malignancy	7.9%	6.0%
Bloody dyscrasias	5.0%	4.1%
Rheumatoid arthritis	4.9%	3.8%
Bleeding disorders	4.0%	3.3%
Asthma	2.9%	2.2%

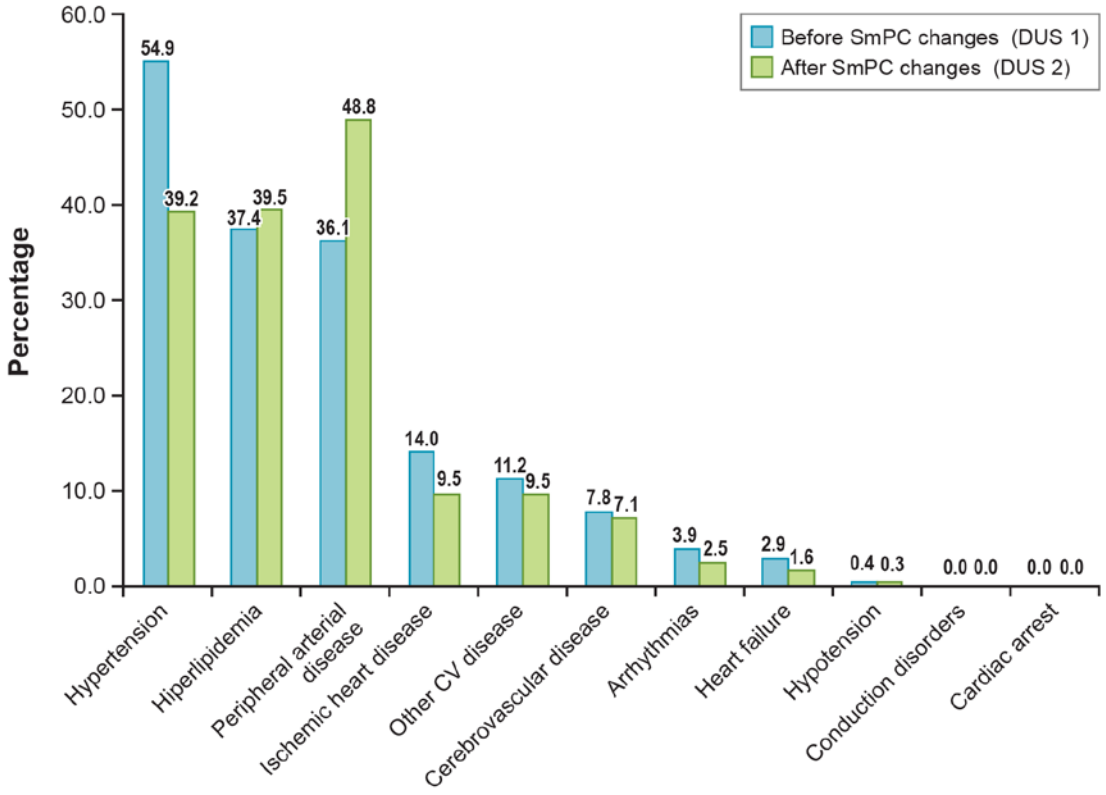
Comorbidities	Before the SmPC changes DUS 1 (N = 4,024)	After the SmPC changes DUS 2 (N = 367)
Peptic ulcer disease	2.1%	1.6%
Liver disease	1.6%	2.7%
HIV	0.3%	0.5%
Connective tissue diseases	0.0%	0.0%

COPD = chronic obstructive pulmonary disease; DUS = drug utilisation study; HIV = human immunodeficiency virus; SmPC = summary of product characteristics.

[a] Excluding diseases of arteries, arterioles, and capillaries.

The prevalence of cardiovascular conditions before and after the SmPC changes is presented in Figure 9. Hypertension was the most frequent cardiovascular condition in the period before the SmPC changes (54.9% before vs. 39.2% after), while peripheral arterial disease was the most frequent condition in the period after the SmPC changes (36.1% before vs. 48.8% after). Other conditions were similar in both periods: hyperlipidemia (37.4% before vs. 39.5% after) and cerebrovascular disease (7.8% before vs. 7.1% after). Ischaemic heart disease was more frequent in the period before the SmPC changes (14.0%) than the period after (9.5%).

Figure 9. Baseline Cardiovascular Comorbidity (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; EpiChron, Aragón, Spain



CV = cardiovascular; DUS = drug utilisation study; SmPC = summary of product characteristics.

The baseline use of comedications before and after the 2013 SmPC changes is presented in Table 22 (EpiChron, Table 9). The most frequent comedications (> 10% of users) in both periods were cardiovascular drugs, proton pump inhibitors, antithrombotics, musculoskeletal system drugs, drugs used in diabetes, respiratory medications, and antidepressants.

After the SmPC changes, there was a higher proportion of users of cardiovascular medications (80.3% before vs. 86.5% after) and antithrombotic agents (52.7% before vs. 57.2% after), and a lower proportion of users of musculoskeletal system drugs (34.3% before vs. 29.4% after).

Table 22. Baseline Use of Comedications (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; EpiChron, Aragón, Spain

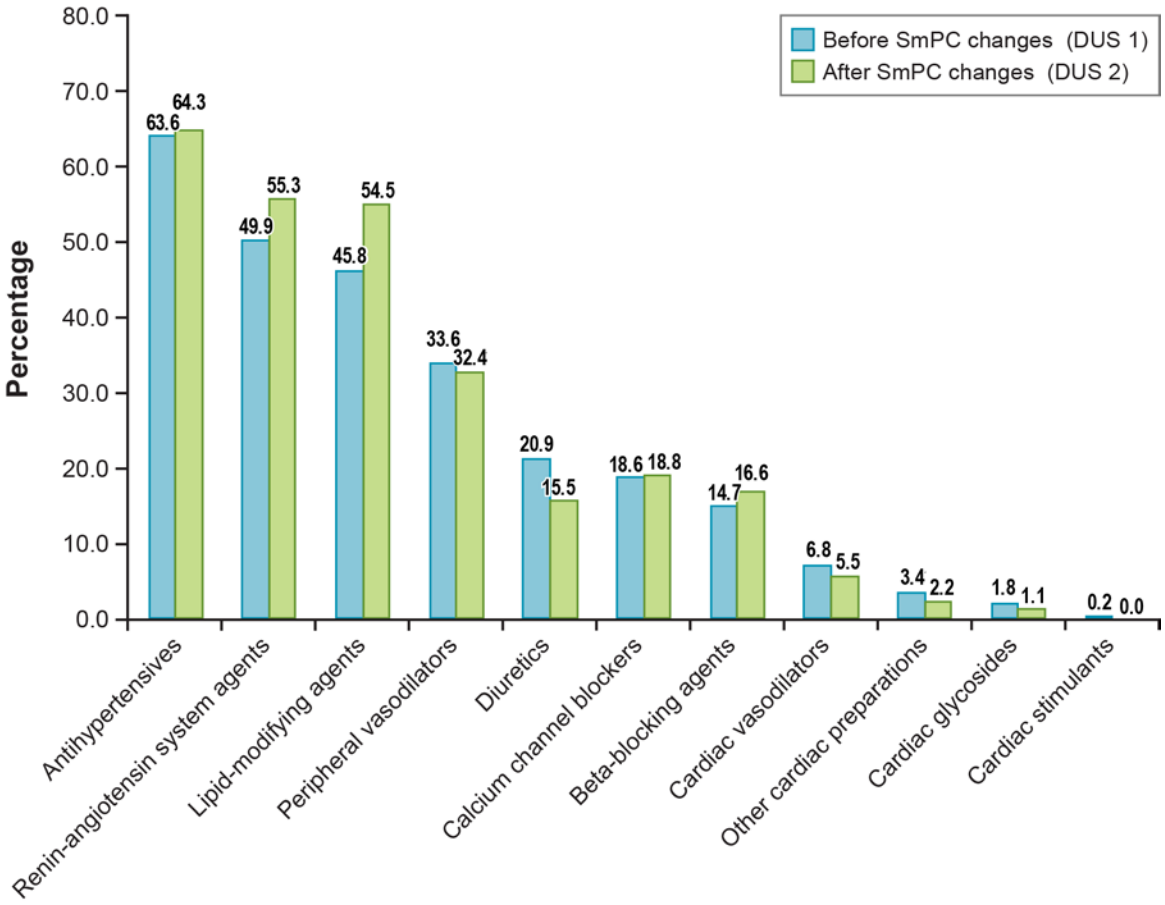
Comedications	Before the SmPC Changes DUS 1 (N = 4,024)	After the SmPC Changes DUS 2 (N = 367)
Cardiovascular medications	80.3	85.6
Proton pump inhibitors	53.2	50.7
Antithrombotic agents	52.7	57.2
Platelet aggregation inhibitors	46.9	54.2
Vitamin K antagonists	5.3	2.7
Heparins	3.6	1.4
Musculoskeletal system drugs	34.3	29.4
Drugs used in diabetes	27.3	30.8
Blood glucose–lowering drugs	20.9	26.7
Insulins	11.8	12.3
Obstructive airway disease drugs	12.7	12.5
Antidepressants	10.8	11.2
Systemic corticosteroids	5.7	7.9
Iron preparations	4.7	5.5
Immunosuppressants	0.7	0.8
Hormone replacement therapy	0.5	0.0
Antineoplastic agents	0.5	1.1
Antivirals	0.2	0.3
Antinicotinics	0.0	0.0

DUS = drug utilisation study; SmPC = summary of product characteristics.

The use of cardiovascular medications before and after the SmPC changes is presented in Figure 10. Antihypertensives, renin-angiotensin system agents, and lipid-modifying agents were the most frequent comedications before and after the 2013 SmPC changes. Other frequent cardiovascular medications were peripheral vasodilators, diuretics, calcium channel blockers, and beta-blocking agents. After the SmPC changes, the use of renin-angiotensin system agents (49.9% before vs. 55.3% after) and lipid-modifying

agents (45.8% before vs. 54.5% after) increased, and the use of diuretics (20.9% before vs. 15.5% after) decreased.

Figure 10. Baseline Use of Cardiovascular Comedications (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; EpiChron, Aragón, Spain



DUS = drug utilisation study; SmPC = summary of product characteristics.

10.2.4.3 Concurrent Use of Potentially Interacting Medications

See file EpiChron_Results_Tables.xlsx, Tables 10 through 13, and 27 for further detailed results.

The concurrent use of potentially interacting comedications before and after the 2013 SmPC changes is presented in Table 23 (EpiChron, Table 13). The proportion of users concurrently treated with potentially interacting medications was similar before and after the SmPC changes (82.5% before vs. 79.0% after). In both periods, the concurrent use of interacting medications was higher for drugs interacting with the CYP2C19 enzyme than for those interacting with the CYP3A4 enzyme.

The concurrent use of CYP3A4 and CYP2C19 potent inhibitors at the start date decreased from 6.4% of users before to 2.2% of users after the SmPC changes. Concurrent use at

the start date and/or during continuous use of cilostazol also decreased after the SmPC changes (10.2% before vs. 3.0% after).

Table 23. Concurrent Use of Potentially Interacting Medications (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; EpiChron, Aragón, Spain

Interaction Medications	Before the SmPC Changes DUS 1 (N = 4,024)	After the SmPC Changes DUS 2 (N = 367)
Any interaction medication	82.5	79.0
Drugs interacting with CYP2C19	71.7	61.3
Substrates	71.4	61.3
Inhibitors	53.7	44.4
Drugs interacting with CYP3A4	57.2	55.6
Substrates	56.0	54.8
Inhibitors	10.5	5.7
Inducers	1.6	0.5
Potent inhibitors	10.2	3.0
CYP2C19 potent inhibitors	7.9	1.9
CYP3A4 potent inhibitors	2.6	1.1

DUS = drug utilisation study; SmPC = summary of product characteristics.

Note: Potent CYP3A4 or CYP2C19 inhibitors were lansoprazole, fluvoxamine, nefazodone, ticlopidine, clarithromycin, troleandomycin, indinavir, ritonavir, nelfinavir, mibefradil, ketoconazole, and itraconazole.

The most frequently prescribed medications interacting with the CYP3A4 enzyme before and after the SmPC changes were atorvastatin, simvastatin, amlodipine, and diltiazem. (Table 24), and the most frequently prescribed medications interacting with the CYP2C19 enzyme were omeprazole, clopidogrel, and pantoprazole (Table 25). After the SmPC changes, there was a lower proportion of users of clopidogrel (23.4% before vs. 17.2% after), pantoprazole (17.1% before vs. 9.3% after), and lansoprazole (7.8% before vs. 1.9% after).

Table 24. Concurrent Use of Cilostazol and Medications Interacting With the CYP3A4 Enzyme (Proportion), Before and After the 2013 SmPC Changes; EpiChron, Aragón, Spain

Interaction Medication	Before the SmPC Changes DUS 1 (N = 4,024)	After the SmPC Changes DUS 2 (N = 367)
Atorvastatin	26.8	24.8
Simvastatin	17.6	21.5
Amlodipine	7.7	7.6
Diltiazem	5.5	4.1
Alprazolam	4.1	3.8
Diazepam	3.6	2.2

Interaction Medication	Before the SmPC Changes DUS 1 (N = 4,024)	After the SmPC Changes DUS 2 (N = 367)
Nifedipine	3.5	1.6
Amiodarone	2.1	1.1
Clarithromycin	2.1	0.8
Pioglitazone	1.0	0.3
Verapamil	0.7	0.0
Haloperidol	0.6	0.5
Erythromycin	0.6	0.0
Tacrolimus	0.3	0.8
Cyclosporine	0.3	0.3
Carbamazepine	0.2	0.3
Phenytoin	0.2	0.0
Felodipine	0.1	0.0
Tamoxifen	0.1	0.0
Aripiprazole	0.0	0.5
Buspirone	0.0	0.0
Cisapride	0.0	0.0
Imatinib	0.0	0.0
Quinine	0.0	0.0
Methadone	0.0	0.0
Sildenafil	0.0	0.0
Triazolam	0.0	0.0

DUS = drug utilisation study; SmPC = summary of product characteristics;

Table 25. Concurrent Use of Cilostazol and Medications Interacting With the CYP2C19 Enzyme (Proportion), Before and After the 2013 SmPC Changes; EpiChron, Aragón, Spain

Interaction Medication	Before the SmPC Changes DUS 1 (N = 4,024)	After the SmPC Changes DUS 2 (N = 367)
Omeprazole	47.7	42.5
Clopidogrel	23.4	17.2
Pantoprazole	17.1	9.3
Lansoprazole	7.8	1.9
Diazepam	3.6	2.2
Amitriptyline	1.8	1.1
Fluoxetine	1.4	1.1
Ketoconazole	0.2	0.0
Phenytoin	0.2	0.0
Clomipramine	0.2	0.0
Ticlopidine	0.1	0.0
Cyclophosphamide	0.0	0.0

DUS = drug utilisation study; SmPC = summary of product characteristics.

The proportion of users concurrently treated with four or more interacting medications at the start date and/or during follow-up decreased after the 2013 SmPC changes (11.6% before vs. 4.4% after). The proportion of users treated with three interacting medications was 17.2% before and 13.9% after; two interacting medications, 26.3% and 27.3%; and a single interacting medication, 27.4% and 33.5% (EpiChron, Table 27).

10.2.4.4 Concurrent Use and Discontinuation of Antithrombotic Agents

See file EpiChron_Results_Tables.xlsx, Tables 14, 15, and 16, for further detailed results.

The proportion of users of cilostazol concurrently treated with antithrombotic agents at the start date and/or during follow-up increased from 68.8% before to 73.3% after the SmPC changes. For concurrent use of cilostazol and platelet aggregation inhibitors, the increase was from 62.3% to 69.2%. The most frequently prescribed platelet aggregation inhibitors were acetylsalicylic acid (41.6% before vs. 54.0% after) and clopidogrel (23.4% before vs. 17.2% after) (EpiChron, Table 15).

Discontinuation of platelet aggregation inhibitors in the 60 days after the start of cilostazol increased from 18.8% of cilostazol users before to 60.0% after the SmPC changes. In the sensitivity analysis, when the period to assess discontinuation of platelet aggregation inhibitors was reduced to 30 days, the discontinuation of platelet aggregation inhibitors increased from 20.1% to 60.9%. When the period to assess

discontinuation was extended to 90 days, the discontinuation of platelet aggregation inhibitors increased from 18.4% to 61.8% (EpiChron, Table 16).

10.2.4.5 Evaluation of Changes to the Summary of Product Characteristics

See file EpiChron_Results_Tables.xlsx, Tables 17 through 20, for further detailed results.

In this section, we present the frequency of conditions included in the new cilostazol SmPC before and after implementation of the 2013 changes in the SmPC. Conditions evaluated were smoking status at the start date, monitoring of patients after 3 months of initiating treatment, discontinuation of cilostazol, old and new contraindications, monitoring of patients at high risk of cardiovascular events, and reduction of daily dose from 200 mg to 100 mg in patients concurrently treated with interacting medications.

Smoking Status at the Start Date

The proportion of users that were current smokers at the start date decreased from 15.9% before to 8.2% after the SmPC changes (EpiChron, Table 17A).

Monitoring of Patients After 3 Months to Evaluate Inadequate Effect of Cilostazol

For both periods, before and after the 2013 SmPC changes, visits to the GP and to specialists were evaluated for the period from 2 months to 4 months after the start date among patients who continued using cilostazol within 3 months after the start date.

The evaluation of visits between 2 months and 4 months after the start date, before and after the 2013 SmPC changes, is presented in Table 26 (EpiChron, Tables 17B and 17C). After the SmPC changes, 161 patients (43.9%) were treated with cilostazol 3 months after the start date. The proportion of patients with a GP or specialist visit decreased from 83.6% before to 31.1% after the SmPC changes. The proportion of patients with a visit related to intermittent claudication or peripheral arterial disease increased from 21.3% to 24.2%.

Table 26. Evaluation of Visits Between 2 Months and 4 Months After the Start Date to Evaluate Inadequate Effect of Cilostazol, Before and After the 2013 SmPC Changes; EpiChron, Aragón, Spain

	Before the SmPC Changes DUS 1 (n = 967)		After the SmPC Changes DUS 2 (n = 161)	
Type of Visit	**n**	**%**	**n**	**%**
GP only	609	63.0	11	6.8
Related to IC/PAD	7	0.7	0	0.0
Unrelated/unknown	602	62.3	11	6.8
Specialist[a]	199	20.6	39	24.2
Vascular clinic	110	11.4	27	16.8
Diabetic clinic	43	4.5	5	3.1
Cardiology clinic	60	6.2	12	7.5

Type of Visit	Before the SmPC Changes DUS 1 (n = 967)		After the SmPC Changes DUS 2 (n = 161)	
	n	%	n	%
Patients without visits	159	16.4	111	68.9
Total GP and/or specialist[b]	808	83.6	50	31.1
Total GP related to IC/PAD or specialist	206	21.3	39	24.2

DUS = drug utilisation study; GP = general practitioner; IC = intermittent claudication; PAD = peripheral arterial disease; SmPC = summary of product characteristics.

[a] Evaluation of visits was based on discharge codes for hospital inpatient and hospital outpatient clinics only. Primary care and other clinics data are not available.

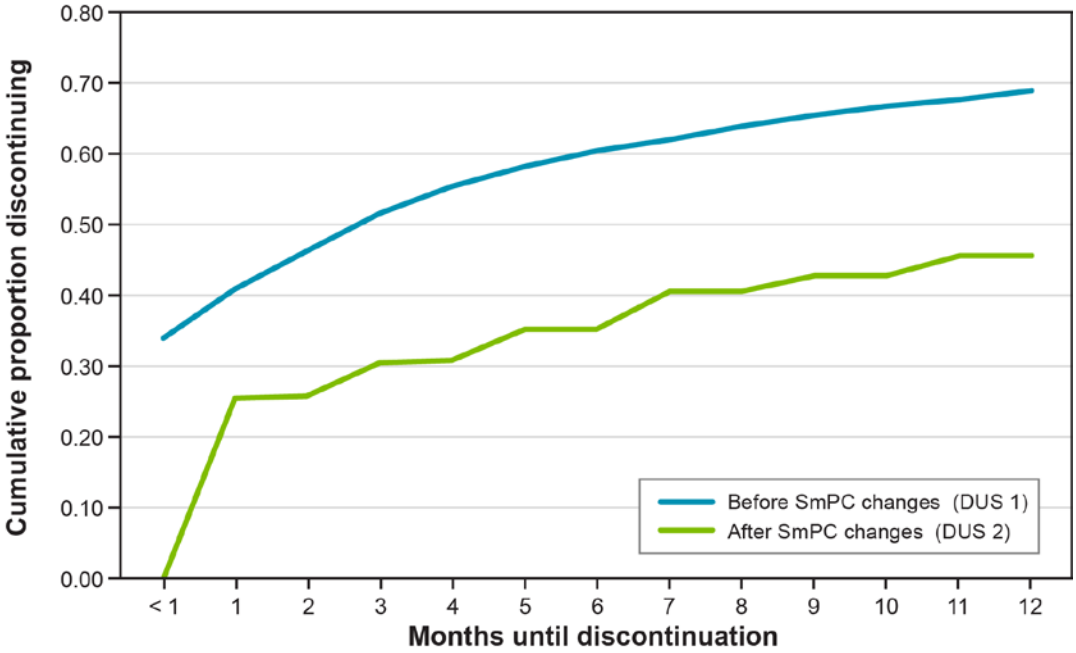
[b] Patients could have visits to more than one specialist and could also have one or more visits to the GP.

In a sensitivity analysis evaluating the period between 1 month and 6 months after the start date, the proportion of patients with a GP and/or specialist visit decreased from 94.5% before to 54.0% after the SmPC changes. The proportion of patients with a visit related to intermittent claudication or peripheral arterial disease increased from 41.5% to 47.8% (EpiChron, Table 17C).

Discontinuation of Cilostazol

Results from the survival analysis of the cumulative proportion of patients discontinuing cilostazol, by month, before and after the 2013 SmPC changes are presented in Figure 11 (EpiChron, Table 17A).

Figure 11. Survival Analysis of Cilostazol Discontinuation Among New Users of Cilostazol Before and After the 2013 SmPC Changes, by Month; EpiChron, Aragón, Spain



DUS = drug utilisation study; SmPC = summary of product characteristics.

A lower proportion of patients discontinued cilostazol in the first month of treatment after the SmPC changes (33.9% before vs. 0% after). The proportion discontinuing in the first 3 months of treatment decreased from 51.9% before to 30.4% after the SmPC changes, and the proportion discontinuing in the first 6 months decreased from 60.5% to 35.2%. The proportion discontinuing in the first 12 months of treatment was also lower in the period after the SmPC changes (69.1% before vs. 45.8% after).

Contraindications

In Table 27, we present the number and proportion of users of cilostazol who had contraindications at the start of cilostazol treatment before and after the SmPC changes. Contraindications evaluated were those included in the labelling before the SmPC revision in 2013 (old contraindications) and those added in the labelling in the SmPC 2013 revision (new contraindications) (EpiChron Tables 17A, 20, 28).

The proportion of patients with old contraindications was approximately 6% before and after the SmPC changes. The proportion of users with new contraindications decreased from 14.3% before to 7.4% after the SmPC changes. Cardiovascular contraindications decreased from 1.7% before to 0.3% after the SmPC changes. Concurrent use of cilostazol and two or more platelet aggregation inhibitors decreased from 13.5% to 7.4%. Overall, the proportion of patients with contraindications (old and/or new) decreased from 19.4% before to 12.5% after the SmPC changes.

Table 27. Contraindications Before and After the 2013 SmPC Changes; EpiChron, Aragón, Spain

	Before the SmPC Changes DUS 1 (N = 4,024)		After the SmPC Changes DUS 2 (N = 149)	
Contraindication	**Number of Patients**	**Proportion**	**Number of Patients**	**Proportion**
Old contraindications (before 2013 SmPC revision)	**249**	**6.2**	**20**	**5.5**
Renal failure	0	0.0	0	0.0
Liver disease	63	1.6	10	2.7
Heart failure	118	2.9	6	1.6
Conditions predisposing to bleeding	70	1.7	5	1.4
Active peptic ulcer	3	0.1	0	0.0
Recent cerebral haemorrhage	0	0.0	0	0.0
Proliferative diabetic retinopathy	67	1.7	5	1.4
Poorly controlled hypertension	0	0.0	0	0.0
Arrhythmias	9	0.2	0	0.0
Ventricular tachycardia	9	0.2	0	0.0
Ventricular fibrillation or multifocal ventricular ectopics	0	0.0	0	0.0
Prolongation of the QT interval	0	0.0	0	0.0

	Before the SmPC Changes DUS 1 (N = 4,024)		After the SmPC Changes DUS 2 (N = 149)	
Contraindication	**Number of Patients**	**Proportion**	**Number of Patients**	**Proportion**
New contraindications (2013 SmPC revision)[a]	**575**	**14.3**	**27**	**7.4**
Cardiovascular diagnosis within 6 months before the start date	70	1.7	1	0.3
Myocardial infarction	40	1.0	1	0.3
Unstable angina	30	0.8	0	0.0
Coronary intervention	0	0.0	0	0.0
Concurrent use of cilostazol with two or more platelet aggregation inhibitors				
At the start date	300	7.5	21	5.7
At the start date and/or during continuous use of cilostazol	544	13.5	27	7.4
Any contraindication (old and new)	**781**	**19.4**	**46**	**12.5**

DUS = drug utilisation study; SmPC = summary of product characteristics;

[a] New contraindications were added to labelling in addition to the old contraindications.

Monitoring of Patients at Increased Risk of Serious Cardiac Events

Rates of visits (to a physician) during continuous use of cilostazol were compared between users at increased risk of serious cardiac events and users not at increased risk. Increased risk was defined as a history of arrhythmias, coronary heart disease, or hypotension at any time before the start date.

Among the 367 new users of cilostazol included in DUS 2 (after the SmPC changes), 44 patients were at increased risk of serious cardiovascular events, and 323 patients were not at increased risk.

The rate of visits per 100 person-years in patients at increased risk decreased from 3,390 (95% CI, 3,348-3,432) before to 2,948 (95% CI, 2,747-3,160) after the SmPC changes. The rate in patients not at increased risk was very similar in both periods, from 3,032 (95% CI, 3,013-3,052) before to 3,033 (95% CI, 2,955-3,112) after the SmPC changes. The RR comparing rates of visits between patients at increased risk and patients not at increased risk was 1.12 (95% CI, 1.10-1.13) in the period before the SmPC changes and 0.97 (95% CI, 0.90-1.05) in the period after the SmPC changes (EpiChron, Table 19).

Reduction of Daily Dose in Patients Receiving Potentially Interacting Medications

The proportion of patients treated with interacting medications and cilostazol 200 mg per day at the start date decreased from 23.9% before to 0.4% after the SmPC changes.

During follow-up, there were no patients concurrently treated with interacting medications and a daily dose of 200 mg after the SmPC changes. Before the SmPC changes, the daily dose of 200 mg was reduced in 1 (0.9%) of the 118 patients concurrently treated with interacting medications.

For concurrent use of CYP3A4 or CYP2C19 potent inhibitors, at start date, 6.4% of patients were concurrently treated with a daily dose of cilostazol 200 mg before the SmPC changes, while no patients were concurrently treated after the SmPC changes. During follow-up, none of the patients before or after the SmPC changes were concurrently treated with CYP3A4 or CYP2C19 potent inhibitors and a cilostazol daily dose of 200 mg (EpiChron Table 18B).

Summary of the Evaluation of Changes to the Summary of Product Characteristics

A summary of the evaluation of the 2013 SmPC changes is presented in Table 28. Compared to the period before the SmPC changes, the period after the SmPC changes was characterised by a decrease in the prevalence of smoking at the start date; a similar monitoring of patients for intermittent claudication and a decrease of early discontinuation of cilostazol at the beginning of treatment; a lower prevalence of patients with the new contraindications in the period after the SmPC; a decrease in the concurrent use of cilostazol and two or more platelet aggregation inhibitors; a slight decrease in the monitoring of patients at high risk of severe cardiovascular events; and a decrease in the concurrent use of a high daily dose of cilostazol and interacting medications, including CYP3A4 or CYP2C19 potent inhibitors.

Table 28. Overall Assessment of Variables Affected by the 2013 SmPC, Before and After the SmPC Changes; EpiChron, Aragón, Spain

2013 Changes to the Summary of Product Characteristics	Study Variable	Before the SmPC Changes DUS 1 (N = 4,024) n (%) or Rate (95% CI)	After the SmPC Changes DUS 2 (N = 367) n (%) or Rate (95% CI)
Indication			
Second-line use after lifestyle modifications, including smoking cessation and (supervised) exercise programmes, failed to sufficiently improve symptoms	Current smoking at the start date	639 (15.9)	30 (8.2)
Physician reassessment of patients after 3 months of treatment with a view to discontinuing cilostazol if an inadequate effect is observed	▪ Visit to GP or specialist between 2 and 4 months after the start date	808 (83.6)	50 (31.1)
	▪ Visit related to intermittent claudication	206 (21.3)	39 (24.2)
	▪ Discontinuation before 3 months of treatment (cumulative proportion discontinuing)	51.9%	30.4%
Contraindications			
Unstable angina pectoris, myocardial infarction within the last 6 months, or a coronary intervention in the last 6 months[a]	As described in labelling	70 (1.7)	1 (0.3)
Concomitant treatment with two or more additional platelet aggregation inhibitors (e.g., aspirin, clopidogrel) at the start date and/or during follow-up	As described in labelling	544 (13.5)	27 (7.4%)
Warnings and precautions			
Close monitoring of patients at increased risk for serious cardiac adverse events as a result of increased heart rate, e.g., patients with stable coronary disease or a history of tachyarrhythmias	Rate of visits to GP or specialist per 100 person-years		
	▪ No increased risk	3,032 (3,013-3,052)	3,033 (2,955-3,112)
	▪ Increased risk	3,390 (3,348-3432)	2,948 (2,747-3,160)
	▪ RR increased/no increased risk	1.12 (1.10-1.13)	0.97 (0.90-1.05)

2013 Changes to the Summary of Product Characteristics	Study Variable	Before the SmPC Changes DUS 1 (N = 4,024) n (%) or Rate (95% CI)	After the SmPC Changes DUS 2 (N = 367) n (%) or Rate (95% CI)
Posology			
Reduction of daily dose to 100 mg in patients receiving medicines interacting with CYP3A4 or CYP2C19 enzymes			
Any interacting medication	Concurrent use of cilostazol 200 mg per day and interacting medications[b]	809 (76.9)	1 (3.6)
	▪ At the start date	691 (65.7)	1 (3.6)
	▪ During follow-up	118 (11.2)	0 (0.0)
	Dose reduction after start of an interacting medication during follow-up	1 of 118 (0.9)	NA (0 patients with a daily dose of 200 mg during follow-up)
CYP3A4 or CYP2C19 potent inhibitors[c]	Concurrent use of cilostazol 200 mg per day and potent inhibitors[b]	105 (10.0)	0 (0.0)
	▪ At the start date	72 (6.8)	0 (0.0)
	▪ During follow-up	33 (3.1)	0 (0.0)
	Dose reduction after start of a potent inhibitor during follow-up	0 of 33 (0.0)	NA (0 patients with a daily dose of 200 mg during follow-up)

CI = confidence interval; DUS = drug utilisation study; GP = general practitioner; NA = not applicable; RR = rate ratio; SmPC = summary of product characteristics.

[a] Coronary procedures are not available in EpiChron.

[b] Based on patients with available information on daily dose: 1,052 patients in DUS 1 and 28 patients in DUS 2.

[c] Potent CYP3A4 or CYP2C19 inhibitors: lansoprazole, fluvoxamine, nefazodone, ticlopidine, clarithromycin, troleandomycin, indinavir, ritonavir, nelfinavir, mibefradil, ketoconazole, and itraconazole.

10.2.4.6 Indication and Off-Label Use

See file EpiChron_Results_Tables.xlsx, Table 21, for further detailed results.

The potential indication and off-label use of cilostazol was evaluated through diagnoses and referral codes using ICPC-2 codes in both periods before and after the SmPC changes.

Results from the review are presented in Table 29. The proportion of users considered to have received cilostazol according to the labelling increased from 53.6% before the SmPC changes to 77.4% after the SmPC changes. Potential off-label prescribing of cilostazol decreased in the period after the SmPC changes (7.9% before vs. 0.8% after).

Table 29. Indication and Potential Off-Label Prescribing of Cilostazol—Review Diagnostic Codes, Before and After the 2013 SmPC Changes; EpiChron, Aragón, Spain

	Before the SmPC Changes DUS 1 (N = 4,024)		After the SmPC Changes DUS 2 (N = 367)	
Category and Diagnosis	Number of Users	Proportion	Number of Users	Proportion
On-label diagnosis	2,156	53.6	284	77.4
Potential off-label diagnosis[a]	317	7.9	3	0.8
Other cardiovascular diseases[b]	63	1.6	0	0
Musculoskeletal disorders	15	0.4	0	0
Varices, phlebitis, thrombophlebitis	80	2.0	1	0.3
Leg/arm pain	0	0	2	0.6
Ischaemic heart disease[c]	3	0.1	0	0
Cerebrovascular disease[d]	14	0.3	0	0
Other diagnoses or no diagnosis recorded	1,551	38.5	80	21.8

DUS = drug utilisation study; ICPC-2 = International Classification of Primary Care, Second Edition; SmPC = summary of product characteristics.

[a] Patients can have more than one diagnosis.

[b] Includes the following ICPC-2 codes: K99, Other cardiovascular disease; K29, Other cardiovascular symptoms, complaints.

[c] Includes the following ICPC-2 codes: K75, Acute myocardial infarction; K74, Ischaemic heart disease with angina; K76, Ischaemic heart disease without angina.

[d] Includes the following ICPC-2 codes: K89, Transient cerebral ischaemia; K91, Cerebrovascular disease; K90, Stroke/cerebrovascular accident.

10.2.4.7 Hospitalisations

See file EpiChron_Results_Tables.xlsx, Table 22, for detailed results.

The proportion of patients who had at least one hospitalisation during the period of continuous use of cilostazol increased from 11.5% before to 20.2% after the SmPC changes.

10.3 Results, SIDIAP, Catalonia, Spain

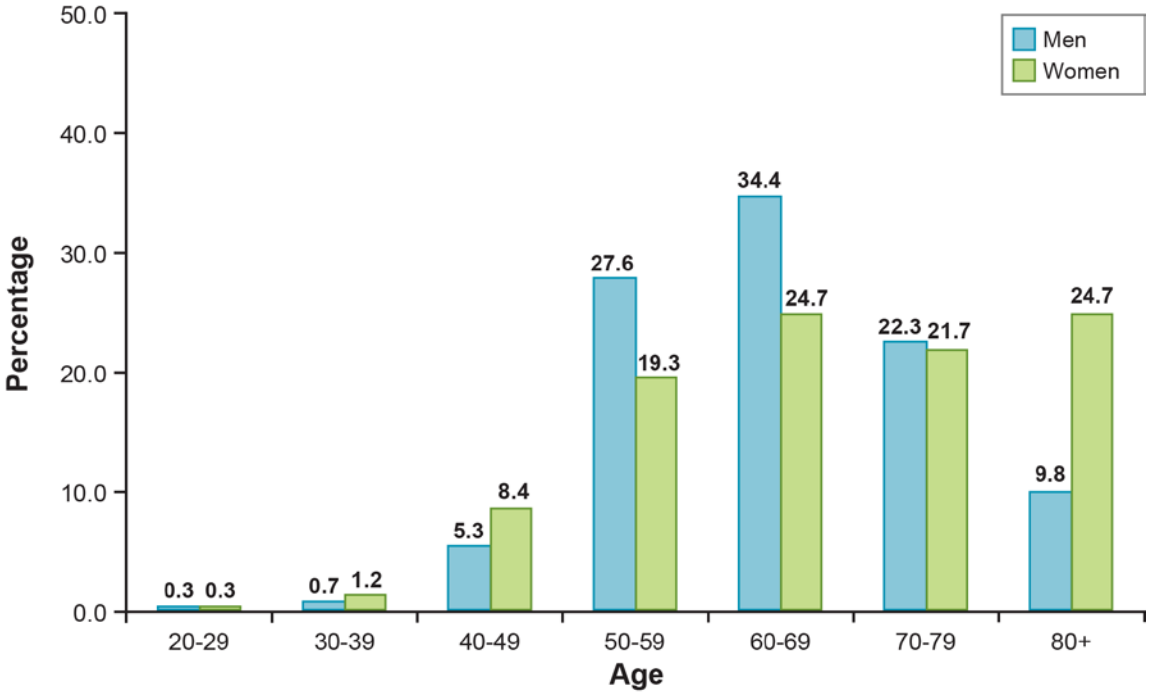
10.3.1 Participants

See file SIDIAP_Results_Tables.xlsx, Tables 1, 4, 25, and 31, for detailed results.

A total of 3,023 patients had a recorded prescription for cilostazol in 2014; of these, 771 (25.5%) patients were new users of cilostazol and were included in the DUS 2 analysis. Only six of these cilostazol new users (0.8%) had less than 1 year of continuous enrolment in SIDIAP.

The age and sex distribution of users at the start date is presented in Figure 12. About 78% of users were men. The median age was 65.0 years, 65.0 years for men and 68.0 years for women (SIDIAP, Table 31); 32.1% of men and 46.4% of women were aged 70 years or older, and 9.8% of men and 24.7% of women were aged 80 years or older (SIDIAP, Table 4).

Figure 12. Age and Sex Distribution of New Users of Cilostazol at the Start Date; SIDIAP, Catalonia, Spain



SIDIAP = Information System for the Improvement of Research in Primary Care database, Catalonia, Spain.

The prevalence of use of cilostazol in SIDIAP in 2014 is presented in Table 30 (SIDIAP, Table 25). The overall prevalence was 64.7 users per 100,000 population. Prevalence was more than five times in men (111.3 per 100,000 population) than in women (20.0 per 100,000 population) and increased by age, especially after 49 years of age. The highest prevalence was for the group aged 70 to 79 years in men and in the group aged 80 years and older in women.

Table 30. Age- and Sex-Specific Prevalence (per 100,000 Population) of Use of Cilostazol During the DUS 2 Study Period; SIDIAP, Catalonia

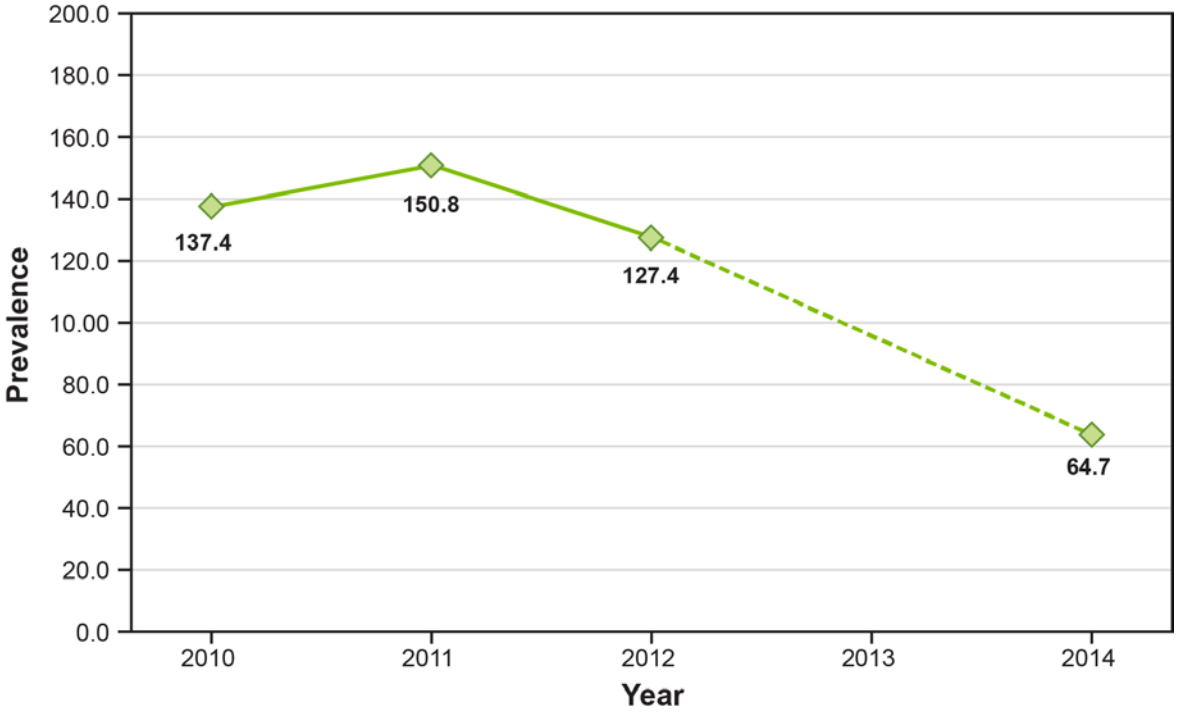
Age in Years	Men	Women	Total
20-29	0.3	0.3	0.3
30-39	1.8	1.5	1.7
40-49	17.7	4.3	11.3
50-59	117.7	19.4	68.3
60-69	312.7	33.2	167.1
70-79	372.3	48.1	195.4
80+	288.7	67.4	148.1
Total	111.3	20.0	64.7

DUS = drug utilisation study; SIDIAP = Information System for the Improvement of Research in Primary Care database, Catalonia, Spain.

Note: Prevalence was calculated using the age and sex distribution of the SIDIAP population in 2014. The study period was from 1 January 2014 until 31 December 2014.

In Figure 13 and Table 31, we present the prevalence of cilostazol use and the demographic characteristics of new users of cilostazol before (DUS 1) and after (DUS 2) implementation of the SmPC changes in 2013. The study period for DUS 1 was from 1 June 2009 to 31 December 2012, and the study period for DUS 2 was from 1 January 2014 to 31 December 2014. The prevalence of use in 2014, after the SmPC changes, was lower than in the 5 preceding years contributing complete annual data to the study (2010 to 2012) (Figure 13). The proportion of men was similar in the two periods, approximately 78% of both users and new users were younger in the period after the SmPC changes (Table 31).

Figure 13. Annual Prevalence of Use of Cilostazol Before (2010-2012) and After (2014) the 2013 SmPC Changes; SIDIAP, Catalonia, Spain



DUS = drug utilisation study; SIDIAP = Information System for the Improvement of Research in Primary Care database, Catalonia, Spain; SmPC = summary of product characteristics.

Note: Data for the year 2009 are not presented because use of cilostazol was not evaluated for the whole year. Data for 2013 were not evaluated because that was the year the SmPC changes were implemented. Years from 2010 to 2012 correspond to the period before the SmPC changes (DUS 1), and the year 2014 corresponds to the period after the SmPC changes (DUS 2).

Table 31. Number and Age and Sex Distribution of New Users of Cilostazol Before and After the 2013 SmPC Changes; SIDIAP, Catalonia, Spain

Characteristic	Before the SmPC Changes DUS 1 (N = 10,142)	After the SmPC Changes DUS 2 (N = 771)
Study period	1 Jun 2009-31 Dec 2012	1 Jan 2014-31 Dec 2014
Number of new users	10,142	771
Men (%)	77.3%	78.5%
Median age (years)		
All new users	70.0	65.0
Men	68.0	65.0
Women	75.0	68.0
Age (years)		
> 60 (%)	79.2%	67.5%
> 70 men (%)	46.3%	32.1%
> 70 women (%)	67.6%	46.4%
> 80 men (%)	15.0%	9.8%
> 80 women (%)	32.2%	24.7%
MEDEA deprivation index		
1st quintile (least deprivation)	8.7%	10.6%
2nd quintile	14.6%	13.4%
3rd quintile	19.1%	14.9%
4th quintile	19.3%	19.7%
5th quintile (most deprivation)	16.3%	21.0%
Rural	19.9%	15.4%
Index not available	2.1%	4.9%

DUS = drug utilisation study; MEDEA = Mortality in Small Areas of Spain and Socioeconomic and Environmental Inequalities; SmPC = summary of product characteristics.

10.3.2 Descriptive Data

See Section 10.1.4, Main Results.

10.3.3 Outcome Data

Not applicable.

10.3.4 Main Results

10.3.4.1 Utilisation Patterns

See file SIDIAP_Results_Tables.xlsx, Tables 1 through 3, 5 through 7, 26, 29, and 30, for detailed results.

In Table 32, we present the utilisation patterns before and after implementation of the 2013 SmPC changes. The proportion of patients receiving a single prescription of cilostazol increased from 15.9% before to 62.5% after the SmPC changes, and the proportion receiving five or more prescriptions decreased from 65.2% to 0.5% (SIDIAP, Table 29). The cilostazol formulation strength of 50 mg became available in Spain only after the SmPC changes in 2013; therefore, only the strength of 100 mg was included in DUS 1. After the SmPC changes, 38.4% of patients received a strength of 50 mg and 66.8% a strength of 100 mg, during the study period.

Daily dose was not evaluated in SIDIAP because the exact day of dispensing is not recorded in the database.

Table 32. Utilisation Patterns of Cilostazol Before and After the 2013 SmPC Changes; SIDIAP, Catalonia, Spain

Drug Use Characteristic	Before the SmPC Changes DUS 1 (N = 10,142)	After the SmPC Changes DUS 2 (N = 771)
Total number of prescriptions	47,205	1,144
Mean number of prescriptions per user in study period	4.7	1.5
Total number of DDDs in study period	3,738,812	47,628
Mean number of DDDs per user in study period	368.7	61.8
Total number of prescriptions per user in study period		
1	15.9%	62.5%
2-4	18.9%	36.9%
5+	65.2%	0.5%
Proportion of users prescribed 50-mg strength during the study period	N/A	38.4%
Proportion of users prescribed 100-mg strength during the study period	100%	66.8%

DDDs = defined daily doses (as defined by the World Health Organization); DUS = drug utilisation study; N/A = not available; SIDIAP = Information System for the Improvement of Research in Primary Care database, Catalonia, Spain; SmPC = summary of product characteristics.

10.3.4.2 Characterisation of Users

See file SIDIAP_Results_Tables.xlsx, Tables 8, 9, and 24, for further detailed results.

The age and sex distribution of users of cilostazol has been described in Section 10.1.1.

The baseline comorbidity of users of cilostazol before and after the 2013 SmPC changes is presented in Table 33 (SIDIAP, Table 8). In both periods, the most frequent conditions (> 10% of users) were cardiovascular disease, diabetes mellitus, COPD, renal diseases,

and malignancy. Compared with before 2013, after the SmPC changes, a similar proportion of users had a history of cardiovascular disease (82.2% before vs. 83.9% after), diabetes mellitus (40.4% vs. 40.3%), COPD (18.0% vs. 19.1%), peptic ulcer (5.4% vs. 6.0%), asthma (2.0% vs. 2.1%), connective tissue diseases (1.6% vs. 2.2%), and human immunodeficiency virus (HIV) (0.3% vs. 0.4%). Prevalence of renal diseases (16.4% vs. 25.8%), malignancy (10.9% vs. 14.7%), skin disorders (8.7% vs. 16.3%), and rheumatoid arthritis (6.6% vs. 11.3%) was higher after the SmPC changes.

Table 33. Baseline Comorbidity (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; SIDIAP, Catalonia, Spain

Comorbidities	Before the SmPC changes DUS 1 (N = 10,142)	After the SmPC changes DUS 2 (N = 771)
Cardiovascular diseases[a]	82.2	83.9
Diabetes mellitus	40.4	40.3
COPD	18.0	19.1
Renal diseases	16.4	25.8
Malignancy	10.9	14.7
Skin disorders	8.7	16.3
Rheumatoid arthritis	6.6	11.3
Bleeding disorders	5.6	9.7
Peptic ulcer disease	5.4	6.0
Liver disease	3.9	6.9
Bloody dyscrasias	3.7	6.7
Asthma	2.0	2.1
Connective tissue diseases	1.6	2.2
HIV[b]	0.3	0.4

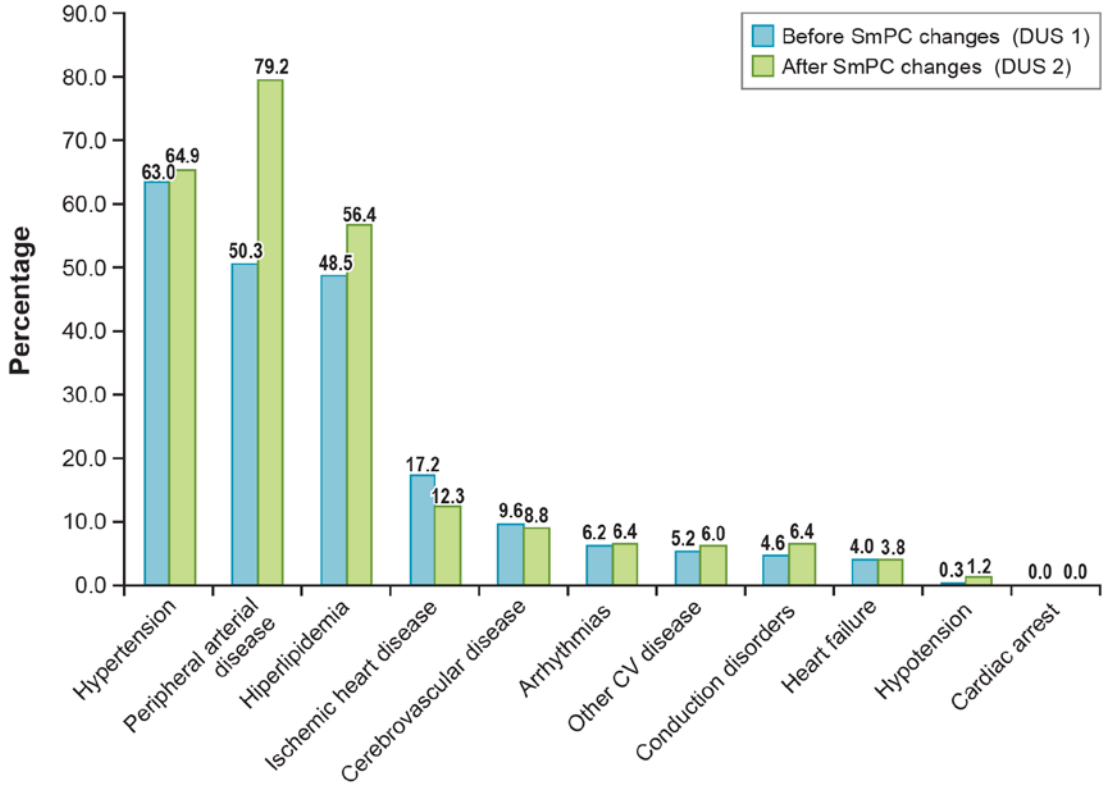
COPD = chronic obstructive pulmonary disease; DUS = drug utilisation study; HIV = human immunodeficiency virus; SIDIAP = Information System for the Improvement of Research in Primary Care database, Catalonia, Spain; SmPC = summary of product characteristics.

[a] Excluding diseases of arteries, arterioles, and capillaries.

[b] Prevalence of HIV is probably underestimated as it is mainly coded in the hospital setting.

The prevalence of cardiovascular conditions before and after the SmPC changes is presented in Figure 14. Hypertension was the most frequent cardiovascular condition in the period before the SmPC changes (63.0%), while peripheral arterial disease was the most frequent cardiovascular condition in the period after the SmPC changes (79.2%), with a lower prevalence in the period before the SmPC changes (50.3%). After the SmPC changes, a higher proportion of users had hyperlipidemia (48.5% before vs. 56.4% after) and a lower proportion of ischaemic heart disease (17.2% before vs. 12.3% after). The prevalence of peripheral arterial disease after the SmPC changes increased. It is important to note that the recording of the ankle-brachial index started in most primary care centres in the years after the SmPC changes.

Figure 14. Baseline Cardiovascular Comorbidity (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; SIDIAP, Catalonia, Spain



CV = cardiovascular; DUS = drug utilisation study; SIDIAP = Information System for the Improvement of Research in Primary Care database, Catalonia, Spain; SmPC = summary of product characteristics.

The baseline use of comedications before and after the 2013 SmPC changes is presented in Table 34 (SIDIAP, Table 9). The most frequent comedications (> 10% of users) in both periods were cardiovascular drugs, antithrombotics, proton pump inhibitors, musculoskeletal system drugs, drugs used in diabetes, respiratory medications, and antidepressants. After the SmPC changes, there was a lower proportion of users of proton pump inhibitors (60.9% before vs. 49.7% after) and musculoskeletal system drugs (39.0% before vs. 19.8% after). The proportion of users of cardiovascular medications, antithrombotic agents, drugs used in diabetes, respiratory medications, and antidepressants was similar in both periods. For antithrombotic agents, the proportion of users of platelet aggregation inhibitors increased after the SmPC changes (73.1% before vs. 80.0% after).

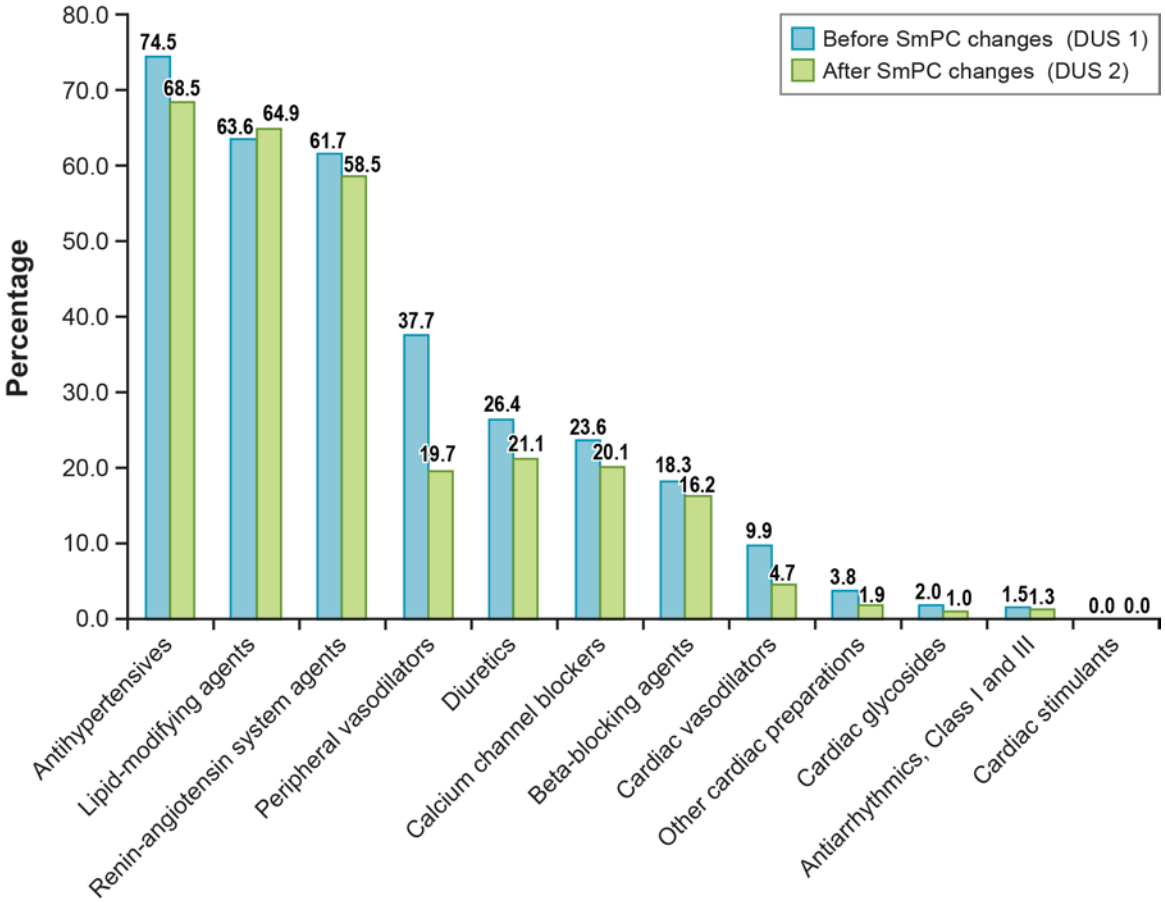
Table 34. Baseline Use of Comedications (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; SIDIAP, Catalonia, Spain

Comedications	Before the SmPC Changes DUS 1 (N = 10,142)	After the SmPC Changes DUS 2 (N = 771)
Cardiovascular medications	90.8	85.0
Antithrombotic agents	77.9	81.2
Platelet aggregation inhibitors	73.1	80.0
Heparins	5.6	5.6
Vitamin K antagonists	4.8	3.2
Proton pump inhibitors	60.9	49.7
Musculoskeletal system drugs	39.0	19.8
Drugs used in diabetes	38.2	35.5
Blood glucose–lowering drugs	32.2	31.9
Insulins	15.5	15.0
Obstructive airway disease drugs	19.8	15.3
Antidepressants	15.6	12.8
Iron preparations	7.2	4.7
Systemic corticosteroids	6.0	5.3
Hormone replacement therapy	1.0	0.3
Antivirals	0.8	0.5
Antineoplastic agents	0.7	0.8
Immunosuppressants	0.5	0.8
Antinicotinics	0.0	0.0

DUS = drug utilisation study; SIDIAP = Information System for the Improvement of Research in Primary Care database, Catalonia, Spain; SmPC = summary of product characteristics.

The baseline use of cardiovascular medications before and after the SmPC changes is presented in Figure 15. Antihypertensives, lipid-modifying agents, and drugs from the renin-angiotensin system were the most frequent baseline comedications before and after the 2013 SmPC changes. Other frequent cardiovascular medications were peripheral vasodilators, diuretics, calcium channel blockers, and beta-blocking agents. After the SmPC changes, the use of antihypertensives (74.5% before vs. 68.5% after), peripheral vasodilators (37.7% before vs. 19.7% after), diuretics (26.4% before vs. 21.1% after), and cardiac vasodilators (9.9% before vs. 4.7% after) decreased.

Figure 15. Baseline Use of Cardiovascular Comedications (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; SIDIAP, Catalonia, Spain



DUS = drug utilisation study; SIDIAP = Information System for the Improvement of Research in Primary Care database, Catalonia, Spain; SmPC = summary of product characteristics.

10.3.4.3 Concurrent Use of Potentially Interacting Medications

See file SIDIAP_Results_Tables.xlsx, Tables 10 through 13, and 27 for further detailed results.

The concurrent use of potentially interacting comedications before and after the 2013 SmPC changes is presented in Table 35 (SIDIAP, Table 13). Most users were concurrently treated with potentially interacting medications in both periods, 90.0% before the SmPC changes and 84.7% after the SmPC changes. In both periods, the concurrent use of interacting medications was higher for drugs interacting with the CYP3A4 enzyme than for those interacting with the CYP2C19 enzyme.

The concurrent use of CYP3A4 and CYP2C19 potent inhibitors at the start date decreased from 4.1% of users before to 1.6% of users after the SmPC changes. Concurrent use at the start date and/or during continuous use of cilostazol also decreased after the SmPC changes (7.3% before vs. 2.1% after).

Table 35. Concurrent Use of Potentially Interacting Medications (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; SIDIAP, Catalonia, Spain

Interaction Medications	Before the SmPC Changes DUS 1 (N = 10,142)	After the SmPC Changes DUS 2 (N = 771)
Any interaction medication	90.0	84.7
Drugs interacting with CYP2C19	75.3	58.6
Substrates	75.0	58.6
Inhibitors	62.2	48.5
Drugs interacting with CYP3A4	73.2	70.9
Substrates	72.2	70.3
Inhibitors	10.2	3.9
Inducers	1.8	1.2
Potent inhibitors	7.3	2.1
CYP2C19 potent inhibitors	4.5	1.3
CYP3A4 potent inhibitors	3.2	0.8

DUS = drug utilisation study; SIDIAP = Information System for the Improvement of Research in Primary Care database, Catalonia, Spain; SmPC = summary of product characteristics.

Note: Potent CYP3A4 or CYP2C19 inhibitors were lansoprazole, fluvoxamine, nefazodone, ticlopidine, clarithromycin, troleandomycin, indinavir, ritonavir, nelfinavir, mibefradil, ketoconazole, and itraconazole.

The most frequently prescribed medications interacting with the CYP3A4 enzyme before and after the SmPC changes were simvastatin, atorvastatin, amlodipine, and diazepam (Table 36), and the most frequently prescribed medications interacting with the CYP2C19 enzyme were omeprazole, clopidogrel, pantoprazole, and diazepam (Table 37). After the SmPC changes, there was a lower proportion of users of most drugs interacting with the CYP2C19 enzyme. The proportion of users of clomipramine (0.4% before vs. 0.3% after), phenytoin (0.4% before vs. 0.1% after), and cyclophosphamide (0.0 both periods) remained similar in both periods.

Table 36. Concurrent Use of Cilostazol and Medications Interacting With the CYP3A4 Enzyme (Proportion), Before and After the 2013 SmPC Changes; SIDIAP, Catalonia, Spain

Interaction Medication	Before the SmPC Changes DUS 1 (N = 10,142)	After the SmPC Changes DUS 2 (N = 771)
Simvastatin	38.0	39.2
Atorvastatin	26.7	24.5
Amlodipine	16.7	15.4
Diazepam	7.1	4.3
Diltiazem	4.3	1.9
Clarithromycin	2.5	0.6
Nifedipine	2.2	1.3

Interaction Medication	Before the SmPC Changes DUS 1 (N = 10,142)	After the SmPC Changes DUS 2 (N = 771)
Amiodarone	1.8	0.5
Trazodone	1.6	1.2
Haloperidol	1.0	0.1
Erythromycin	0.9	0.1
Verapamil	0.7	0.5
Pioglitazone	0.7	0.4
Itraconazole	0.6	0.1
Carbamazepine	0.5	0.6
Phenytoin	0.4	0.1
Tamoxifen	0.1	0.1
Felodipine	0.1	0.0
Buspirone	0.0	0.0
Chlorpheniramine	0.0	0.0
Cimetidine	0.0	0.0
Methadone	0.0	0.0
Quinine	0.0	0.0
Midazolam	0.0	0.0
Rifampicin	0.0	0.0
Cyclosporine	0.0	0.0
Sildenafil	0.0.	0.0

DUS = drug utilisation study; SIDIAP = Information System for the Improvement of Research in Primary Care database, Catalonia, Spain; SmPC = summary of product characteristics.

Table 37. Concurrent Use of Cilostazol and Medications Interacting With the CYP2C19 Enzyme (Proportion), Before and After the 2013 SmPC Changes; SIDIAP, Catalonia, Spain

Interaction Medication	Before the SmPC Changes DUS 1 (N = 10,142)	After the SmPC Changes DUS 2 (N = 771)
Omeprazole	59.3	47.6
Clopidogrel	22.5	11.2
Pantoprazole	9.7	5.8
Diazepam	7.1	4.3
Lansoprazole	4.2	1.3
Rabeprazole	2.9	0.4
Amitriptyline	2.2	1.6
Fluoxetine	2.1	0.3
Clomipramine	0.4	0.3
Phenytoin	0.4	0.1
Cyclophosphamide	0.0	0.0

DUS = drug utilisation study; SIDIAP = Information System for the Improvement of Research in Primary Care database, Catalonia, Spain; SmPC = summary of product characteristics.

The proportion of users concurrently treated with four or more interacting medications decreased from 16.2% before to 5.2% after the 2013 SmPC changes. The proportion of users treated with three interacting medications was 20.6% before and 16.9% after; two interacting medications, 29.3% and 29.3%; and a single interacting medication, 23.9% and 33.3% (SIDIAP, Table 27).

10.3.4.4 Concurrent Use and Discontinuation of Antithrombotic Agents

See file THIN3_Results_Tables.xlsx, Tables 14 through 16, for further detailed results.

The proportion of users concurrently treated with antithrombotic agents at the start date and/or during follow-up increased from 66.2% of users to 81.2% of users after the 2013 SmPC changes. The proportion of users concurrently treated with platelet aggregation inhibitors increased from 62.9% before to 77.8% after the SmPC changes. The most frequently prescribed platelet aggregation inhibitors were acetylsalicylic acid (45.1% before vs. 68.9% after) and clopidogrel (17.7% before vs. 11.2% after) (SIDIAP, Table 15).

Discontinuation of platelet aggregation inhibitors in the 60 days after the start of cilostazol decreased from 8.9% of cilostazol users before to 6.3% after the SmPC changes. In the sensitivity analysis, when the period to assess discontinuation of platelet aggregation inhibitors was reduced to 30 days, the discontinuation of platelet aggregation inhibitors decreased from 20.1% of cilostazol users before to 15.2% after the SmPC changes. When the period of assessment was extended to 90 days, the discontinuation of platelet aggregation inhibitors decreased from 6.6% of cilostazol users before to 2.7% after the SmPC changes (SIDIAP, Table 16).

10.3.4.5 Evaluation of Changes to the Summary of Product Characteristics

See file SIDIAP_Results_Tables.xlsx, Tables 17 through 20, for further detailed results.

In this section, we present the frequency of conditions included in the new cilostazol SmPC before and after implementation of the 2013 changes in the SmPC. Conditions evaluated were smoking status at the start date, monitoring of patients after 3 months of initiating treatment, discontinuation of cilostazol, old and new contraindications, monitoring of patients at high risk of cardiovascular events, and reduction of daily dose from 200 mg to 100 mg in patients concurrently treated with interacting medications.

Smoking Status at the Start Date

The proportion of users that were current smokers at the start date increased from 32.3% before to 45.5% after the SmPC changes (SIDIAP, Table 17A).

Monitoring of Patients After 3 Months to Evaluate Inadequate Effect of Cilostazol

For both periods, before and after the 2013 SmPC changes, visits to the GP and to specialists were evaluated for the period from 2 months to 4 months after the start date among patients who continued using cilostazol within 3 months after the start date.

The evaluation of visits between 2 months and 4 months after the start date, before and after the 2013 SmPC changes, is presented in Table 38 (SIDIAP, Tables 17B and 17C). After the SmPC changes, 397 patients (51.5%) were treated with cilostazol 3 months after the start date. The proportion of patients with a GP or specialist visit decreased from 82.0% to 13.6%, and the proportion of patients with a visit related to intermittent claudication or peripheral arterial disease decreased from 53.5% to 10.8%.

Table 38. Evaluation of Visits Between 2 Months and 4 Months After the Start Date to Evaluate Inadequate Effect of Cilostazol, Before and After the 2013 SmPC Changes; SIDIAP, Catalonia, Spain

	Analysis of ICD-10 Codes			
	Before the SmPC Changes DUS 1 (n = 7,071)		After the SmPC Changes DUS 2 (n = 397)	
Type of Visit	**n**	**%**	**n**	**%**
GP only	5,508	77.9	28	7.1
Related to IC/PAD	3,494	49.4	17	4.3
Unrelated/unknown	2,014	28.5	11	2.8
Specialist[a]	290	4.1	26	6.5
Vascular clinic	132	1.9	24	6.0
Diabetic clinic	32	0.5	1	0.3
Cardiology clinic	136	1.9	3	0.8
Patients without visits	1,273	18.0	343	86.4
Total GP or specialist[a]	5,789	82.0	54	13.6
Total GP related to IC/PAD or specialist	3,784	53.5	43	10.8

DUS = drug utilisation study; GP = general practitioner; IC = intermittent claudication; PAD = peripheral arterial disease; SIDIAP = Information System for the Improvement of Research in Primary Care database, Catalonia, Spain; SmPC = summary of product characteristics.

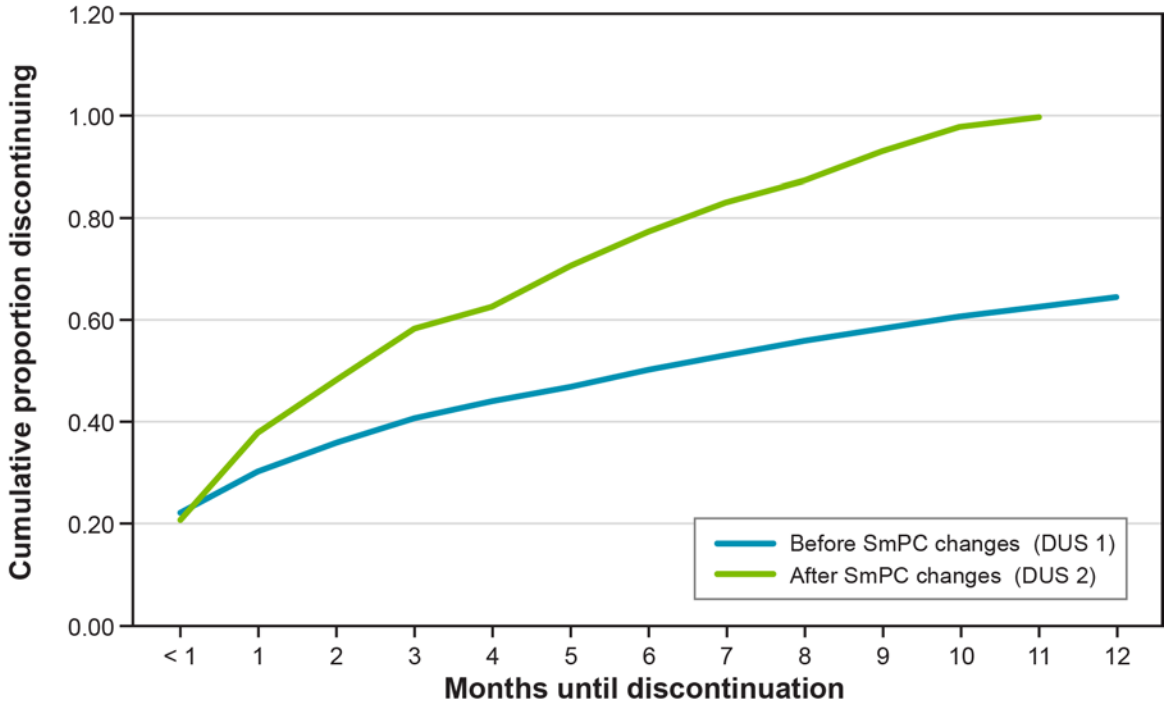
[a] Patients could have visits to more than one specialist and could also have one or more visits to the GP.

In a sensitivity analysis evaluating the period between 1 month and 6 months after the start date, the proportion of patients with a GP or specialist visit decreased from 93.7% before to 30.5% after the SmPC changes, and the proportion of patients with a visit related to intermittent claudication or peripheral arterial disease decreased from 63.0% to 25.4% (SIDIAP, Table 17B [DUS 1] and Table 17C [DUS 2]).

Discontinuation of Cilostazol

Results from the survival analysis of the cumulative proportion of patients discontinuing cilostazol, by month, before and after the 2013 SmPC changes are presented in Figure 16 (SIDIAP, Table 17A).

Figure 16. Survival Analysis of Cilostazol Discontinuation Among New Users of Cilostazol Before and After the 2013 SmPC Changes, by Month; SIDIAP, Catalonia, Spain



DUS = drug utilisation study; SIDIAP = Information System for the Improvement of Research in Primary Care database, Catalonia, Spain; SmPC = summary of product characteristics.

The proportion of patients discontinuing cilostazol in the first month of treatment increased from 30.3% before to 37.7% after the SmPC changes. The proportion discontinuing in the first 3 months of treatment increased from 40.6% before to 58.1% after the SmPC changes, and the proportion discontinuing in the first 6 months of treatment increased from 50.4% before to 77.3% after the SmPC changes.

Contraindications

In Table 39, we present the number and proportion of users of cilostazol who had contraindications at the start of cilostazol treatment before and after the SmPC changes. Contraindications evaluated were those included in the labelling before the SmPC revision in 2013 (old contraindications) and those added in the labelling in the SmPC 2013 revision (new contraindications).

The proportion of patients with old contraindications increased from 42.0% before to 51.5% after the SmPC changes. The proportion of users with new contraindications decreased from 8.7% before to 6.7% after the SmPC changes. Cardiovascular

contraindications decreased from 3.0% before to 0.9% after the SmPC changes. Concurrent use of cilostazol and two or more platelet aggregation inhibitors was similar in both periods. Overall, the proportion of patients with contraindications (old and/or new) increased from 46.6% before to 55.1% after the SmPC changes (SIDIAP, Table 17A, Table 20, Table 28).

Table 39. Contraindications Before and After the 2013 SmPC Changes; SIDIAP, Catalonia, Spain

	Before the SmPC Changes DUS 1 (N = 10,142)		After the SmPC Changes DUS 2 (N = 771)	
Contraindication	**Number of Patients**	**Proportion**	**Number of Patients**	**Proportion**
Old contraindications (before 2013 SmPC revision)	**4,258**	**42.0**	**397**	**51.5**
Renal failure	806	7.9	100	13.0
Liver disease	376	3.7	53	6.9
Heart failure	377	3.7	29	3.8
Conditions predisposing to bleeding	3,035	29.9	297	38.5
Active peptic ulcer	7	0.1	3	0.4
Recent cerebral haemorrhage	23	0.2	0	0.0
Proliferative diabetic retinopathy	453	4.5	58	7.5
Poorly controlled hypertension	2,698	26.6	263	34.1
Arrhythmias	601	5.9	1	0.1
Ventricular tachycardia	2	0.02	1	0.1
Ventricular fibrillation or multifocal ventricular ectopics	1	0.01	1	0.0
Prolongation of the QT interval	0	0.0	NR	NR

	Before the SmPC Changes DUS 1 (N = 10,142)		After the SmPC Changes DUS 2 (N = 771)	
Contraindication	**Number of Patients**	**Proportion**	**Number of Patients**	**Proportion**
New contraindications (2013 SmPC revision)[a]	**883**	**8.7**	**52**	**6.7**
Cardiovascular diagnosis within 6 months before the start date	302	3.0	7	0.9
Myocardial infarction	170	1.7	1	0.1
Unstable angina	102	1.0	1	0.1
Coronary intervention	48	0.5	6	0.8
Concurrent use of cilostazol with two or more platelet aggregation inhibitors				
At the start date	381	3.8	33	4.3
At the start date and/or during continuous use of cilostazol	641	6.3	19	2.5
Any contraindication (old and new)	**4,730**	**46.6**	**425**	**55.1**

DUS = drug utilisation study; NR = not reported; SIDIAP = Information System for the Improvement of Research in Primary Care database, Catalonia, Spain; SmPC = summary of product characteristics.

[a] New contraindications were added to labelling in addition to the old contraindications.

Monitoring of Patients at Increased Risk of Serious Cardiac Events

Rates of visits (to a physician) during continuous use of cilostazol were compared between users at increased risk of serious cardiac events and users not at increased risk. Increased risk was defined as a history of arrhythmias, coronary heart disease, or hypotension at any time before the start date.

Among the 771 new users of cilostazol included in DUS 2 (after the SmPC changes), 139 (18.0%) patients were at increased risk of serious cardiovascular events, and 632 (82.0%) patients were not at increased risk.

The rate of visits per 100 person-years in patients at increased risk increased from 565.3 (95% CI, 555.8-575.4) before to 748.9 (95% CI, 704.8-795.8) after the SmPC changes. The rate in patients not at increased risk decreased from 474.9 (95% CI, 470.1-479.7) before to 428.2 (95% CI, 412.3-444.6) after the SmPC changes. The RR comparing rates of visits between patients at increased risk and patients not at increased risk was

1.19 (95% CI, 1.17-1.22) in the period before the SmPC changes and 1.75 (95% CI, 1.63-1.88) in the period after the SmPC changes.

Reduction of Daily Dose in Patients Receiving Potentially Interacting Medications

In SIDIAP, reduction of daily dose was not evaluated because the exact day of dispensing is not recorded in the database.

Summary of the Evaluation of Changes to the Summary of Product Characteristics

A summary of the evaluation of the 2013 the SmPC changes is presented in Table 40. Compared to the period before the SmPC changes, the period after the SmPC changes was characterised by a higher prevalence of smoking at the start date; a decrease in the monitoring of patients after the start of treatment; an increase in early discontinuation of cilostazol; a lower prevalence of patients with the new contraindications; similar concurrent use of cilostazol and two or more platelet aggregation inhibitors; and an increase in the monitoring of patients at high risk of severe cardiovascular events.

Table 40. Overall Assessment of Variables Affected by the 2013 SmPC, Before and After the SmPC Changes; SIDIAP, Catalonia, Spain

2013 Changes to the Summary of Product Characteristics	Study Variable	Before the SmPC Changes DUS 1 (N = 10,142) n (%) or Rate[a] (95% CI)	After the SmPC Changes DUS 2 (N = 771) n (%) or Rate[a] (95% CI)
Indication			
Second-line use after lifestyle modifications, including smoking cessation and (supervised) exercise programmes, failed to sufficiently improve symptoms	Current smoking at the start date	2,973 (32.3)	340 (45.5)
Physician reassessment of patients after 3 months of treatment with a view to discontinuing cilostazol if an inadequate effect is observed	▪ Visit to GP or specialist between 2 and 4 months after the start date	5,798 (82.0)[a]	54 (13.6)[b]
	▪ Visit related to intermittent claudication	3,784 (53.5)[a]	43 (10.8)[b]
	▪ Discontinuation before 3 months of treatment (cumulative proportion discontinuing)[c]	40.6	58.1
Contraindications			
Unstable angina pectoris, myocardial infarction within the last 6 months, or a coronary intervention in the last 6 months	As described in labelling	302 (3.0)	7 (0.9)
Concomitant treatment with two or more additional platelet aggregation inhibitors (e.g., aspirin, clopidogrel) at the start date and/or during follow-up	As described in labelling	641 (6.3)	47 (6.1)
Warnings and precautions			
Close monitoring of patients at increased risk for serious cardiac adverse events as a result of increased heart rate, e.g., patients with stable coronary disease or a history of tachyarrhythmias	Rate of visits to GP or specialist per 100 person-years		
	▪ No increased risk	474.9 (470.1-479.7)	428.2 (412.3-444.6)
	▪ Increased risk	565.3 (555.8-575.4)	748.9 (704.8-795.8)
	▪ RR increased/no increased risk	1.19 (1.17-1.22)	1.75 (1.63-1.88)
Posology			
Reduction of daily dose to 100 mg in patients receiving medicines interacting with CYP3A4 or CYP2C19 enzymes		N/A (daily dose not available)	N/A (daily dose not available)

CI = confidence interval; DUS = drug utilisation study; GP = general practitioner; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th Revision; N/A = not available; RR = rate ratio; SIDIAP = Information System for the Improvement of Research in Primary Care database, Catalonia, Spain; SmPC = summary of product characteristics.

[a] Based on the analysis of ICD-10 codes of 7,071 patients treated with cilostazol 3 months after the start date.

[b] Based on the analysis of ICD-10 codes of all patients in DUS 2 treated with cilostazol 3 months after the start date (N = 397).

[c] Cumulative proportion of patients discontinuing calculated using survival analysis.

10.3.4.6 Indication and Off-Label Use

See file SIDIAP_Results_Tables.xlsx, Table 21, for further detailed results.

In DUS 1, we evaluated the potential indication and off-label prescribing of cilostazol using diagnostic codes and review of free text in a random sample of 195 patients. In DUS 2, free text was not available in SIDIAP, and we evaluated the indication of cilostazol using diagnostic codes only (Table 41).

Potential off-label prescribing of cilostazol decreased from 10.3% of users before to 6.4% after the SmPC changes. The proportion of users with a specific diagnosis of intermittent claudication before initiating cilostazol was higher after the SmPC changes (73.2%) than before the SmPC changes (24.1%).

Table 41. Indication and Potential Off-Label Prescribing of Cilostazol Before and After the 2013 SmPC Changes; SIDIAP, Catalonia, Spain

	Before the SmPC Changes DUS 1 (N = 195)[a]		After the SmPC Changes DUS 2 (N = 777)[b]	
Category and Diagnosis	**Number of Users**	**Proportion**	**Number of Users**	**Proportion**
On-label diagnosis[c]	80	41.0	611	79.2
Intermittent claudication[d]	47	24.1	564	73.2
Potential off-label diagnosis	20	10.3	49	6.4
Arterial stenosis	6	3.1	0	0.0
Venous insufficiency/ thrombosis	4	2.1	0	0.0
Leg pain	4	2.1	0	0.0
Cerebrovascular accident	4	2.1	22	2.9
Ischaemic heart disease	2	1.0	21	2.7
Other cardiovascular disease	0	0.0	14	1.8
Other diagnoses or no diagnosis recorded	95	48.7	111	14.4

DUS = drug utilisation study; SIDIAP = Information System for the Improvement of Research in Primary Care database, Catalonia, Spain; SmPC = summary of product characteristics

[a] Based on review of patients profiles.

[b] Based on codes.

[c] Diagnosis of intermittent claudication and/or peripheral arterial disease before the start date.

[d] Diagnosis of intermittent claudication with or without a diagnosis of peripheral arterial disease.

10.3.4.7 Hospitalisations

Data on hospitalisations were not available in SIDIAP.

10.4 Results, National Health Registers, Sweden

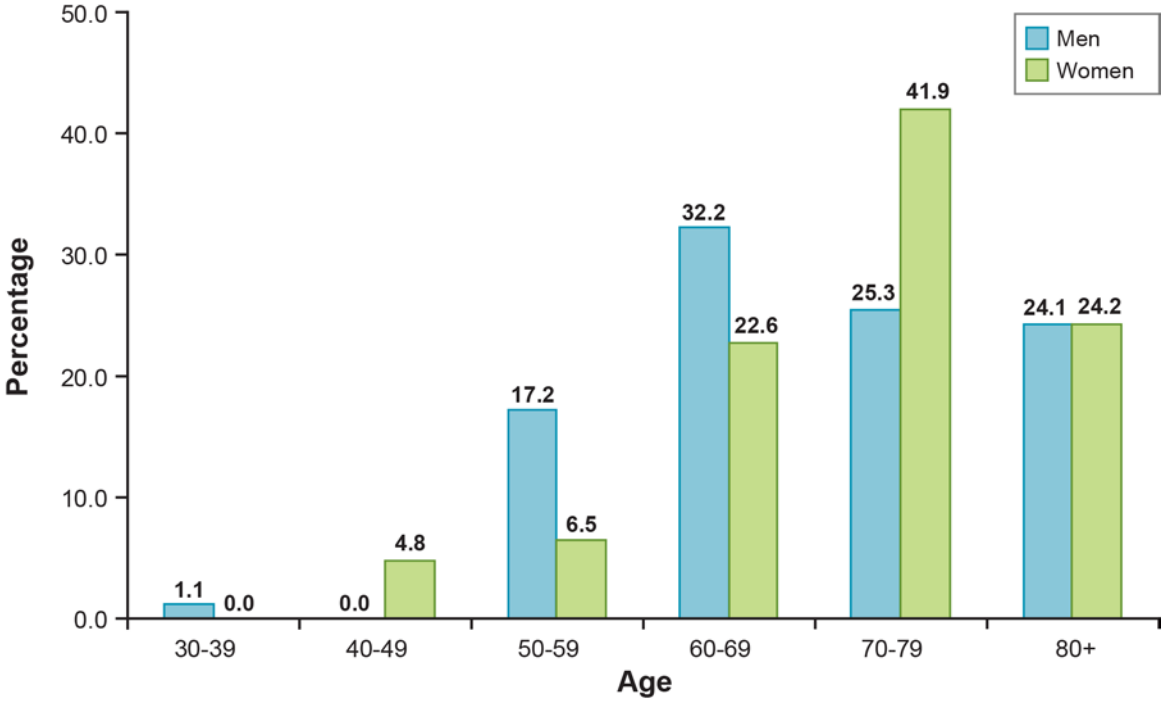
10.4.1 Participants

See file SWEDEN_Results_Tables.xlsx, Tables 1, 4, 24, 25, and 31, for detailed results.

A total of 544 patients had a recorded prescription for cilostazol in 2014; of these, 149 (27.4%) patients were new users of cilostazol and were included in the DUS 2 analysis. None of these new users of cilostazol had less than 1 year of continuous enrolment in the Swedish registers.

The age and sex distribution of new users at the start date is presented in Figure 17. About 58% of new users were men. The median age was 71.0 years, 69.7 years for men and 72.5 years for women (Sweden, Table 31); 49.4% of men and 66.1% of women were aged 70 years or older, and 24.1% of men and 24.2% of women were aged 80 years or older (Sweden, Table 4).

Figure 17. Age and Sex Distribution of New Users of Cilostazol at the Start Date; National Registers, Sweden



The prevalence of use of cilostazol (new and prevalent users) in Sweden in 2014 is presented in Table 42 (Sweden, Table 25). The overall prevalence was 7.2 users per 100,000 population. Prevalence was higher in men (8.0 per 100,000 population) than in women (6.4 per 100,000 population) and increased by age, especially after 59 years of age in men and after 69 years of age in women. The highest prevalence was for the group aged 80+ years in men and for the group 70 to 79 years in women.

Table 42. Age- and Sex-Specific Prevalence (per 100,000 Population) of Use of Cilostazol During the DUS 2 Study Period; National Registers, Sweden

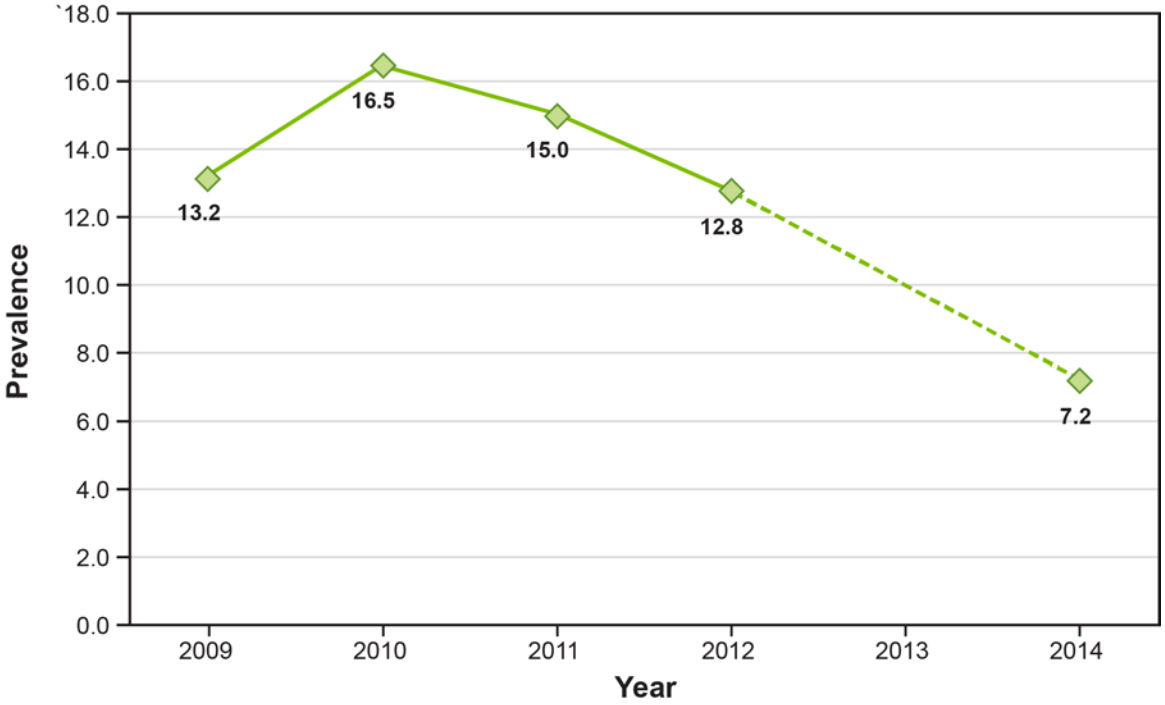
Age in Years	Men	Women	Total
30-39	0.3	0.0	0.2
40-49	0.3	0.6	0.5
50-59	5.1	3.2	4.2
60-69	16.3	8.9	12.6
70-79	27.7	24.5	26.0
80+	32.6	21.4	25.6
Total	8.0	6.4	7.2

DUS = drug utilisation study.

Note: Prevalence was calculated using the age and sex distribution of the population in Sweden in 2014. The study period was from 1 January 2014 until 31 December 2014. There were no users of cilostazol below the age of 30 years.

In Figure 18 and Table 43, we present the prevalence of cilostazol use and the demographic characteristics of new users of cilostazol before (DUS 1) and after (DUS 2) implementation of the SmPC changes in 2013. The study period for DUS 1 was from 20 March 2008 to 31 December 2012, and the study period for DUS 2 was from 1 January 2014 to 31 December 2014. The prevalence of use in 2014, after the SmPC changes, was lower than in the 4 preceding years contributing complete annual data to the study (2009 to 2012) (Figure 18). After the SmPC changes, the proportion of men was slightly higher, and new users, especially women, were slightly older.

Figure 18. Annual Prevalence of Use of Cilostazol Before (2009-2012) and After (2014) the 2013 SmPC Changes; National Registers, Sweden



DUS = drug utilisation study; SmPC = summary of product characteristics.

Note: Data for the year 2008 are not presented because use of cilostazol was not evaluated for the whole year. Data for 2013 were not evaluated because that was the year the SmPC changes were implemented. Years from 2008 to 2012 correspond to the period before the SmPC changes (DUS 1), and the year 2014 corresponds to the period after the SmPC changes (DUS 2).

Table 43. Number and Age and Sex Distribution of New Users of Cilostazol Before and After the 2013 SmPC Changes; National Registers, Sweden

Characteristic	Before the SmPC Changes DUS 1 (N = 2,887)	After the SmPC Changes DUS 2 (N = 149)
Study period	20 Mar 2008-31 Dec 2012	1 Jan 2014-31 Dec 2014
Number of new users	2,887	149
Men (%)	52.3%	58.4%
Median age (years)		
All	73.7	71.0
Men	72.4	69.7
Women	75.0	72.5
Age (years)		
> 60 (%)	90.0%	84.6%
> 70 men (%)	58.7%	49.4%
> 70 women (%)	69.0%	66.1%
> 80 men (%)	22.5%	24.1%
> 80 women (%)	31.2%	24.2%
Income		
1st quintile (lowest)	17.8%	19.5%
2nd quintile	23.7%	20.1%
3rd quintile	23.3%	20.1%
4th quintile	20.7%	20.1%
5th quintile (highest)	No data	20.1%
Index not available	14.5%	0%
Education		
< 9 years	37.9%	40.9%
9-12 years	33.4%	36.9%
>12 years	12.9%	18.8%
Not available	15.9%	3.4%

DUS = drug utilisation study; SmPC = summary of product characteristics.

10.4.2 Descriptive Data

See Section 10.1.4, Main Results.

10.4.3 Outcome Data

Not applicable.

10.4.4 Main Results

10.4.4.1 Utilisation Patterns

See file SWEDEN_Results_Tables.xlsx, Tables 1 through 3, 5 through 7, 26, 29, and 30, for detailed results.

In Table 44, we present the utilisation patterns before and after implementation of the 2013 SmPC changes. The proportion of patients dispensed a single prescription of cilostazol increased from 42.0% before to 47.0% after the SmPC changes, and the proportion receiving five or more dispensings decreased from 28.8% to 15.4%. Prescribing of the 50-mg and 100-mg strength was similar before and after the SmPC changes: 23.4% of users before the SmPC changes and 21.5% of users after the SmPC changes received the strength of 50 mg, and about 81% received the strength of 100 mg in both periods (Sweden, Table 1). The proportion of users receiving a daily dose of 100 mg or 200 mg was similar before and after the SmPC changes. In both periods, before and after SmPC changes, approximately 20% of users received a daily dose of 100 mg, and 80% received a daily dose of 200 mg.

Table 44. Utilisation Patterns of Cilostazol Before and After the 2013 SmPC Changes; National Registers, Sweden

Drug Use Characteristic	Before the SmPC Changes DUS 1 (N = 2,887)	After the SmPC Changes DUS 2 (N = 149)
Total number of dispensings	11,295	282
Mean number of dispensings per user in study period	3.91	1.89
Total number of DDDs in study period	613,897	14,492
Mean number of DDDs per user in study period	212.6	97.26
Total number of dispensings per user in study period		
1	42.0%	47.0%
2-4	29.2%	37.6%
5+	28.8%	15.4%
Proportion of users dispensed 50-mg strength during the study period	23.4%	21.5%
Proportion of users dispensed 100-mg strength during the study period	81.0%	80.5%
Daily dose at the start date		
100 mg	21.9%	20.1%
200 mg	78.1%	79.9%
Other	No data	No data

DDDs = defined daily doses (as defined by the World Health Organization); DUS = drug utilisation study; SmPC = summary of product characteristics;

10.4.4.2 Characterisation of Users

See file Sweden_Results_Tables.xlsx, Tables 8 and 9 for further detailed results.

The age and sex distribution of users of cilostazol has been described in Section 10.1.1.

The baseline comorbidity of users of cilostazol before and after the 2013 SmPC changes is presented in Table 45 (Sweden, Table 8). In both periods, the most frequent conditions (> 10% of users) were cardiovascular disease, renal diseases, bleeding disorders, diabetes mellitus, and malignancy. Compared with before the SmPC changes, after the SmPC changes, a similar proportion of users had a history of cardiovascular disease (62.8% before vs. 63.8% after), renal diseases (15.8% before vs. 15.4% after), and malignancies (16.7% before vs. 17.4% after). Prevalence of skin disorders (7.8% before vs. 12.8% after) was higher after the SmPC changes.

Table 45. Baseline Comorbidity (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; National Registers, Sweden

Comorbidities	Before the SmPC changes DUS 1 (N = 2,887)	After the SmPC changes DUS 2 (N = 149)
Cardiovascular diseases[a]	62.8%	63.8%
Skin disorders	7.8%	12.8%
Renal diseases	15.8%	15.4%
Bleeding disorders	11.7%	15.4%
Diabetes mellitus	20.5%	20.1%
Asthma	3.7%	4.7%
Malignancy	16.7%	17.4%
COPD	8.6%	8.1%
Peptic ulcer disease	3.5%	2.7%
Bloody dyscrasias	5.6%	8.1%
Rheumatoid arthritis	5.0%	4.7%
Liver disease	1.0%	1.3%
Connective tissue diseases	3.3%	3.4%
HIV	0.0%	0.7%

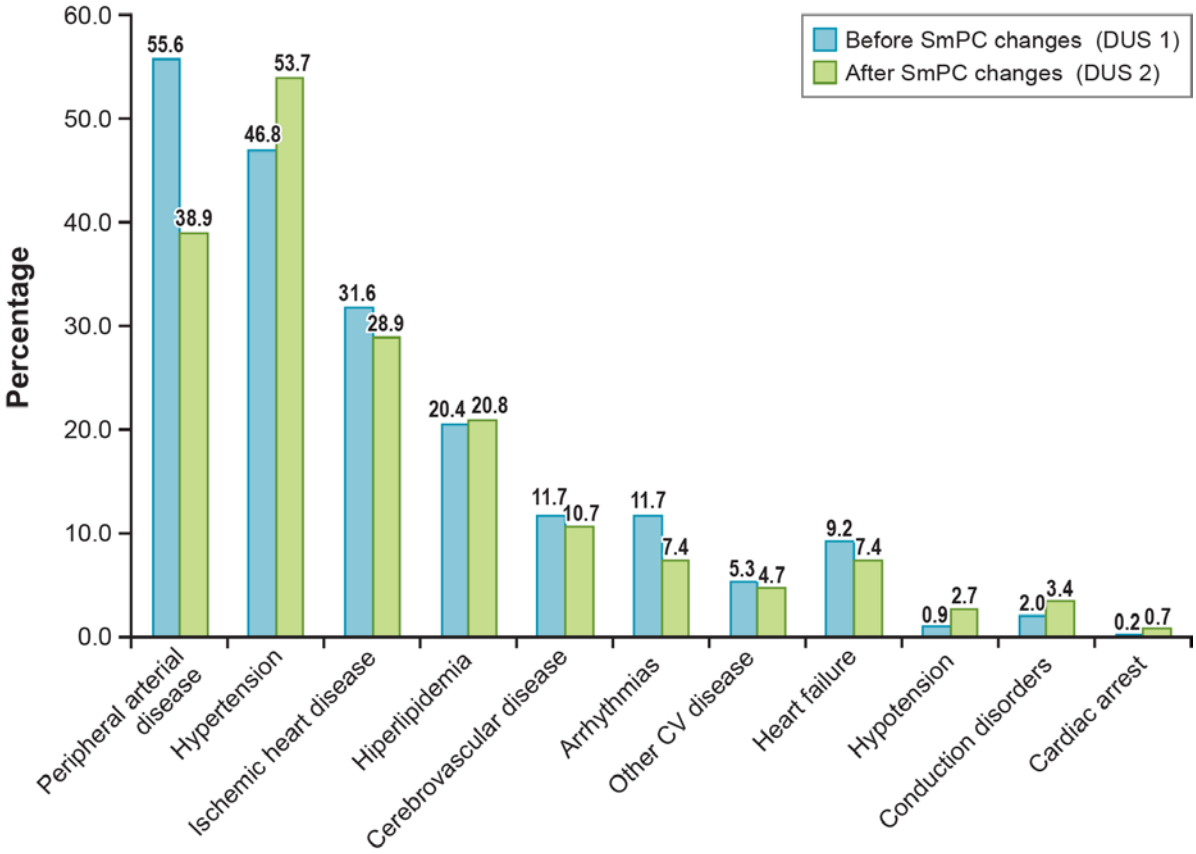
COPD = chronic obstructive pulmonary disease; DUS = drug utilisation study; HIV = human immunodeficiency virus; SmPC = summary of product characteristics.

[a] Excluding diseases of arteries, arterioles, and capillaries.

The prevalence of cardiovascular conditions before and after the SmPC changes is presented in Figure 19. Peripheral arterial disease was the most frequent cardiovascular condition in the period before the SmPC changes (55.6% before vs. 38.9% after), while hypertension was the most frequent condition in the period after the SmPC changes (46.8% before vs. 53.7% after). Other conditions were similar in both periods: ischaemic heart disease (31.6% before vs. 28.9% after), hyperlipidemia (20.4% before vs. 20.8% after), and cerebrovascular disease (11.7% before vs. 10.7% after). Arrhythmias were

more frequent in the period before the SmPC changes (11.7%) than the period after (7.4%).

Figure 19. Baseline Cardiovascular Comorbidity (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; National Registers, Sweden



CV = cardiovascular; DUS = drug utilisation study; SmPC = summary of product characteristics.

The baseline use of comedications before and after the 2013 SmPC changes is presented in Table 46 (Sweden, Table 9). The most frequent comedications (> 10% of users) in both periods were cardiovascular drugs, antithrombotics, proton pump inhibitors, musculoskeletal system drugs, respiratory medications, antidepressants, and drugs used in diabetes. After the SmPC changes, there was a higher proportion of users of proton pump inhibitors (22.4% before vs. 26.2% after), and a lower proportion of users of musculoskeletal system drugs (19.4% before vs. 12.1% after). The proportion of users of cardiovascular medications, antithrombotic agents, respiratory medications, and antidepressants was similar in both periods. For antithrombotic agents, the proportion of users of platelet aggregation inhibitors decreased after the SmPC changes (69.7% before vs. 59.1% after).

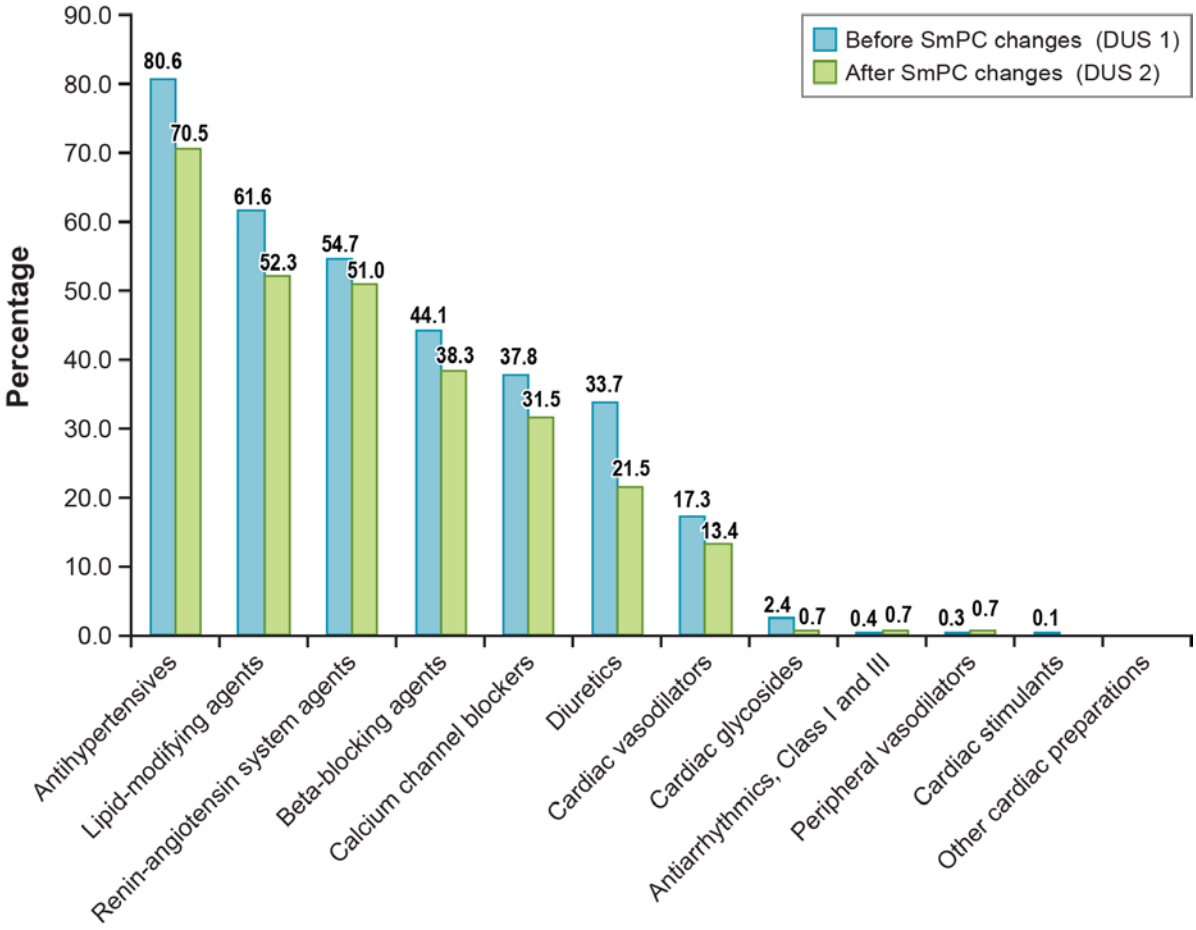
Table 46. Baseline Use of Comedications (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; National Registers, Sweden

Comedications	Before the SmPC Changes DUS 1 (N = 2,887)	After the SmPC Changes DUS 2 (N = 149)
Cardiovascular medications	88.5	79.9
Antithrombotic agents	73.3	62.4
Platelet aggregation inhibitors	69.7	59.1
Vitamin K antagonists	4.4	2.7
Heparins	2.2	0.7
Proton pump inhibitors	22.4	26.2
Musculoskeletal system drugs	19.4	12.1
Obstructive airway disease drugs	15.1	12.1
Antidepressants	13.6	18.1
Drugs used in diabetes	21.9	22.1
Blood glucose–lowering drugs	16.4	16.1
Insulins	11.2	11.4
Antinicotinics	2.8	2.7
Systemic corticosteroids	6.9	6.7
Iron preparations	2.9	3.4
Hormone replacement therapy	8.4	3.4
Antineoplastic agents	0.6	2.0
Immunosuppressants	1.2	1.3
Antivirals	1.0	2.0

DUS = drug utilisation study; SmPC = summary of product characteristics.

The baseline use of cardiovascular medications before and after the SmPC changes is presented in Figure 20. Antihypertensives and lipid-modifying agents were the most frequent comedications before and after the 2013 SmPC changes. Other frequent cardiovascular medications were renin-angiotensin system agents, calcium channel blockers, diuretics, and beta-blocking agents. After the SmPC changes, the use of antihypertensives (80.7% before vs. 70.5% after) and diuretics (33.7% before vs. 21.5% after) decreased, and the use of lipid-modifying agents (61.6% before vs. 52.3% after) and beta-blocking agents (44.1% before vs. 38.3% after) increased.

Figure 20. Baseline Use of Cardiovascular Comedications (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; National Registers, Sweden



DUS = drug utilisation study; SmPC = summary of product characteristics.

10.4.4.3 Concurrent Use of Potentially Interacting Medications

See file Sweden_Results_Tables.xlsx, Tables 10 through 13, and 27 for further detailed results.

The concurrent use of potentially interacting comedications before and after the 2013 SmPC changes is presented in Table 47 (Sweden, Table 13). The proportion of users concurrently treated with potentially interacting medications decreased from 84.4% before to 79.9% after the SmPC changes. In both periods, the concurrent use of interacting medications was higher for drugs interacting with the CYP3A4 enzyme than for those interacting with the CYP2C19 enzyme.

The concurrent use of CYP3A4 and CYP2C19 potent inhibitors at the start date decreased from 1.3% of users before to 0.7% of users after the SmPC changes. Concurrent use at the start date and/or during continuous use of cilostazol also decreased after the SmPC changes (2.7% before vs. 0.7% after).

Table 47. Concurrent Use of Potentially Interacting Medications (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; National Registers, Sweden

Interaction Medications	Before the SmPC Changes DUS 1 (N = 1,528)	After the SmPC Changes DUS 2 (N = 104)
Any interaction medication	84.4	79.9
Drugs interacting with CYP2C19	37.4	30.9
Substrates	36.6	30.2
Inhibitors	25.6	20.1
Drugs interacting with CYP3A4	78.2	71.1
Substrates	77.6	71.1
Inhibitors	4.4	2.7
Inducers	1.5	1.3
Potent inhibitors	2.7	0.7
CYP2C19 potent inhibitors	1.2	0.7
CYP3A4 potent inhibitors	1.5	0.0

DUS = drug utilisation study; SmPC = summary of product characteristics.

Note: Potent CYP3A4 or CYP2C19 inhibitors were lansoprazole, fluvoxamine, nefazodone, ticlopidine, clarithromycin, troleandomycin, indinavir, ritonavir, nelfinavir, mibefradil, ketoconazole, and itraconazole.

The most frequently prescribed medications interacting with the CYP3A4 enzyme before and after the SmPC changes were simvastatin, amlodipine, felodipine, and atorvastatin (Table 48), and the most frequently prescribed medications interacting with the CYP2C19 enzyme were omeprazole and clopidogrel (Table 49). After the SmPC changes, there was a lower proportion of users of omeprazole (23.6% before vs. 18.8% after) and clopidogrel (11.7% before vs. 7.4% after).

Table 48. Concurrent Use of Cilostazol and Medications Interacting With the CYP3A4 Enzyme (Proportion), Before and After the 2013 SmPC Changes; National Registers, Sweden

Interaction Medication	Before the SmPC Changes DUS 1 (N = 2,887)	After the SmPC Changes DUS 2 (N = 149)
Simvastatin	55.7	38.9
Amlodipine	18.5	21.5
Felodipine	18.5	11.4
Atorvastatin	10.1	23.5
Diazepam	3.3	2.7
Sildenafil	1.6	3.4
Diltiazem	1.5	1.3
Nifedipine	1.3	0.7
Cisapride	1.1	2.0
Alprazolam	1.1	0.7

Interaction Medication	Before the SmPC Changes DUS 1 (N = 2,887)	After the SmPC Changes DUS 2 (N = 149)
Verapamil	1.1	0.0
Carbamazepine	0.8	0.0
Quinine	0.7	1.3
Erythromycin	0.6	0.7
Pioglitazone	0.5	1.3
Phenytoin	0.4	0.0
Clarithromycin	0.3	0.0
Amiodarone	0.2	0.7
Tamoxifen	0.2	0.7
Cyclosporine	0.2	0.0
Triazolam	0.2	0.0
Imatinib	0.1	0.0
Aripiprazole	0.1	0.0
Buspirone	0.1	0.0
Haloperidol	0.1	0.0
Methadone	0.1	0.0
Tacrolimus	0.0	0.7

DUS = drug utilisation study; SmPC = summary of product characteristics;

Table 49. Concurrent Use of Cilostazol and Medications Interacting With the CYP2C19 Enzyme (Proportion), Before and After the 2013 SmPC Changes; National Registers, Sweden

Interaction Medication	Before the SmPC Changes DUS 1 (N = 2,887)	After the SmPC Changes DUS 2 (N = 149)
Omeprazole	23.6	18.8
Clopidogrel	11.7	7.4
Diazepam	3.3	2.7
Amitriptyline	2.5	4.0
Pantoprazole	1.4	3.4
Lansoprazole	1.1	0.7
Ketoconazole	0.8	0.0
Fluoxetine	0.6	0.7
Phenytoin	0.4	0.0
Clomipramine	0.4	0.0
Ticlopidine	0.2	0.0
Cyclophosphamide	0.1	0.0

DUS = drug utilisation study; SmPC = summary of product characteristics.

The proportion of users concurrently treated with four or more interacting medications was very similar before (5.6%) and after (5.4%) the 2013 SmPC changes. The proportion of users treated with three interacting medications was 14.1% before and 10.1% after; two interacting medications, 30.2% and 28.2%; and a single interacting medication, 34.5% and 36.2% (Sweden, Table 27).

10.4.4.4 Concurrent Use and Discontinuation of Antithrombotic Agents

See file Sweden_Results_Tables.xlsx, Tables 14, 15, and 16, for further detailed results.

The proportion of users of cilostazol concurrently treated with antithrombotic agents at the start date and/or during follow-up decreased from 77.9% before to 69.1% after the SmPC changes. For concurrent use of cilostazol and platelet aggregation inhibitors, the decrease was from 74.3% to 65.1%. The most frequently prescribed platelet aggregation inhibitors were acetylsalicylic acid (69.6% before vs. 59.7% after) and clopidogrel (10.8% before vs. 7.4% after) (Sweden, Table 15).

Discontinuation of platelet aggregation inhibitors in the 60 days after the start of cilostazol increased from 13.6% of cilostazol users before to 18.4% after the SmPC changes. In the sensitivity analysis, when the period to assess discontinuation of platelet aggregation inhibitors was reduced to 30 days, the discontinuation of platelet aggregation inhibitors increased from 17.4% to 20.7%. When the period to assess discontinuation was extended to 90 days, the discontinuation of platelet aggregation inhibitors increased from 12.4% to 19.5% (Sweden, Table 16).

10.4.4.5 Evaluation of Changes to the Summary of Product Characteristics

See file Sweden_Results_Tables.xlsx, Tables 17 through 20, for further detailed results.

In this section, we present the frequency of conditions included in the new cilostazol SmPC before and after implementation of the 2013 changes in the SmPC. Conditions evaluated were smoking status at the start date, monitoring of patients after 3 months of initiating treatment, discontinuation of cilostazol, old and new contraindications, monitoring of patients at high risk of cardiovascular events, and reduction of daily dose from 200 mg to 100 mg in patients concurrently treated with interacting medications.

Smoking Status at the Start Date

In Sweden, smoking status was evaluated using diagnosis codes for smoking-related disease and use of smoking-cessation drugs. The proportion of users that were current smokers at the start date increased from 3.2% before to 4.0% after the SmPC changes (Sweden, Table 17A).

Monitoring of Patients After 3 Months to Evaluate Inadequate Effect of Cilostazol

For both periods, before and after the 2013 SmPC changes, visits to specialist clinics were evaluated for the period from 2 months to 4 months after the start date among

patients who continued using cilostazol within 3 months after the start date. Information on primary care was not available.

The evaluation of visits between 2 months and 4 months after the start date, before and after the 2013 SmPC changes, is presented in Table 50 (Sweden, Table 17C). After the SmPC changes, 69 patients (46.3%) were treated with cilostazol 3 months after the start date. The proportion of patients with a GP or specialist visit increased from 8.6% before to 13.0% after the SmPC changes. The proportion of patients with a visit related to intermittent claudication or peripheral arterial disease increased from 8.5% to 13.0%.

Table 50. Evaluation of Visits Between 2 Months and 4 Months After the Start Date to Evaluate Inadequate Effect of Cilostazol, Before and After the 2013 SmPC Changes; National Registers, Sweden

	Before the SmPC Changes DUS 1 (n = 1,715)		After the SmPC Changes DUS 2 (n = 69)	
Type of Visit	**n**	**%**	**n**	**%**
GP only	N/A	N/A	N/A	N/A
Related to IC/PAD	N/A	N/A	N/A	N/A
Unrelated/unknown	N/A	N/A	N/A	N/A
Specialist[a]	146	8.5	9	13.0
Vascular clinic	88	5.1	6	8.7
Diabetic clinic	13	0.8	1	1.5
Cardiology clinic	52	3.0	3	4.4
Patients without visits	1,568	91.4	60	87.0
Total specialist visits[b]	147	8.6	9	13.0
Total visits related to IC/PAD specialist	146	8.5	9	13.0

DUS = drug utilisation study; GP = general practitioner; IC = intermittent claudication; N/A = not available; PAD = peripheral arterial disease; SmPC = summary of product characteristics.

[a] Evaluation of visits was based on discharge codes for hospital inpatient and hospital outpatient clinics only. Primary care and other clinics data are not available.

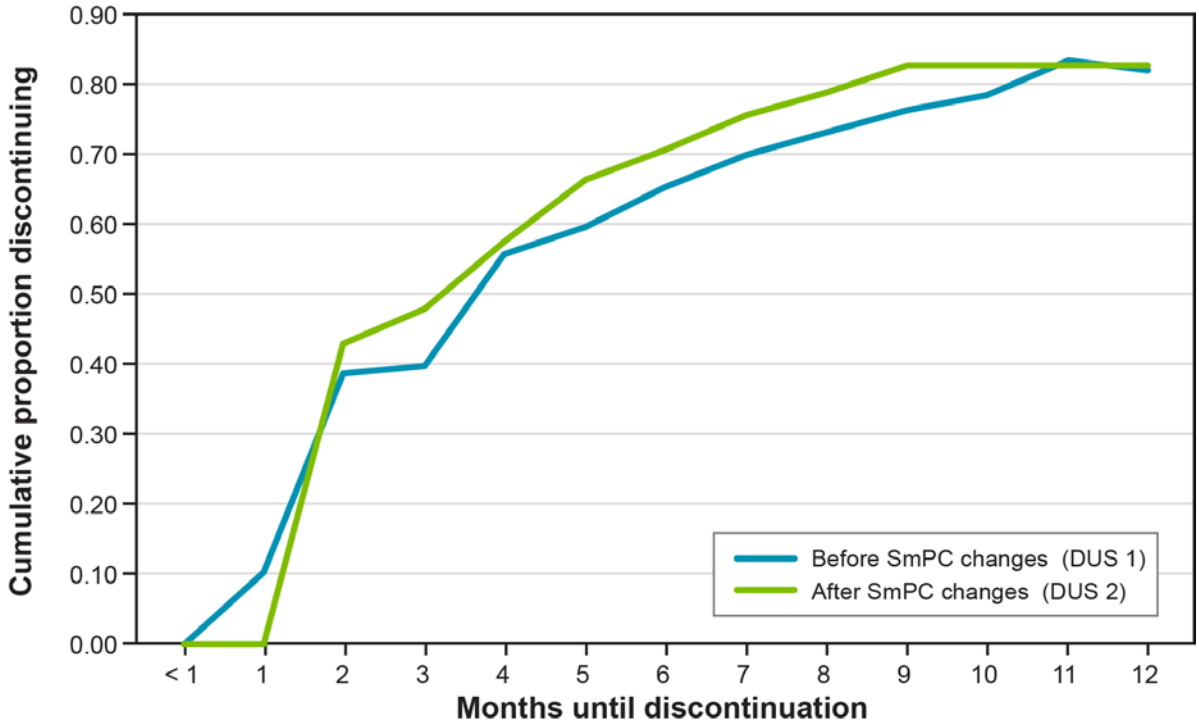
[b] Patients could have visits to more than one specialist.

In a sensitivity analysis evaluating the period between 1 month and 6 months after the start date, the proportion of patients with a specialist visit increased from 16.0% before to 18.8% after the SmPC changes (Sweden, Table 17b).

Discontinuation of Cilostazol

Results from the survival analysis of the cumulative proportion of patients discontinuing cilostazol, by month, before and after the 2013 SmPC changes are presented in Figure 21 (Sweden, Table 17A).

Figure 21. Survival Analysis of Cilostazol Discontinuation Among New Users of Cilostazol Before and After the 2013 SmPC Changes, by Month; National Registers, Sweden



DUS = drug utilisation study; SmPC = summary of product characteristics.

A higher proportion of patients discontinued cilostazol in the first 2 months of treatment after the SmPC changes (38.3% before vs. 43.0% after). The proportion discontinuing in the first 3 months of treatment increased from 39.4% before to 47.9% after the SmPC changes, and the proportion discontinuing in the first 6 months increased from 65.2% to 70.6%. The proportion discontinuing in the first 12 months of treatment was similar before (81.9%) and after (82.6%) the SmPC changes.

Contraindications

In Table 51, we present the number and proportion of users of cilostazol who had contraindications at the start of cilostazol treatment before and after the SmPC changes. Contraindications evaluated were those included in the labelling before the SmPC revision in 2013 (old contraindications) and those added in the labelling in the SmPC 2013 revision (new contraindications) (Sweden Tables 17A, 20, 28).

The proportion of patients with old contraindications was approximately 12% before and after the SmPC changes. The proportion of users with new contraindications decreased

from 12.4% before to 6.7% after the SmPC changes. Cardiovascular contraindications decreased from 5.2% before to 2.7% after the SmPC changes. Concurrent use of cilostazol and two or more platelet aggregation inhibitors decreased from 8.4% to 4.0%. Overall, the proportion of patients with contraindications (old and/or new) decreased from 21.8% before to 18.8% after the SmPC changes.

Table 51. Contraindications Before and After the 2013 SmPC Changes; National Registers, Sweden

	Before the SmPC Changes DUS 1 (N = 2,887)		After the SmPC Changes DUS 2 (N = 149)	
Contraindication	**Number of Patients**	**Proportion**	**Number of Patients**	**Proportion**
Old contraindications (before 2013 SmPC revision)	**351**	**12.2**	**18**	**12.1**
Renal failure	80	2.8	5	3.4
Liver disease	30	1.0	2	1.3
Heart failure	87	3.0	5	3.4
Conditions predisposing to bleeding	165	5.7	9	6.0
Active peptic ulcer	11	0.4	1	0.7
Recent cerebral haemorrhage	4	0.1	0	0.0
Proliferative diabetic retinopathy	150	5.2	8	5.4
Poorly controlled hypertension			0	0.0
Arrhythmias	41	1.4	1	0.7
Ventricular tachycardia	16	0.6	1	0.7
Ventricular fibrillation or multifocal ventricular ectopics	24	0.8	0	0.0
Prolongation of the QT interval	2	0.1	0	0.0
New contraindications (2013 SmPC revision)[a]	**359**	**12.4**	**10**	**6.7**
Cardiovascular diagnosis within 6 months before the start date	151	5.2	4	2.7
Myocardial infarction	44	1.5	4	2.7
Unstable angina	120	4.2	0	0.0
Coronary intervention	37	1.3	1	0.7
Concurrent use of cilostazol with two or more platelet aggregation inhibitors				
At the start date	171	5.9	5	3.4
At the start date and/or during continuous use of cilostazol	243	8.4	6	4.0
Any contraindication (old and new)	**630**	**21.8**	**28**	**18.8**

DUS = drug utilisation study; SmPC = summary of product characteristics.

[a] New contraindications were added to labelling in addition to the old contraindications.

Monitoring of Patients at Increased Risk of Serious Cardiac Events

Rates of visits (to a specialist physician) during continuous use of cilostazol were compared between users at increased risk of serious cardiac events and users not at increased risk. Increased risk was defined as a history of arrhythmias, coronary heart disease, or hypotension at any time before the start date.

Among the 149 new users of cilostazol included in DUS 2 (after the SmPC changes), 47 patients were at increased risk of serious cardiovascular events, and 102 patients were not at increased risk.

The rate of visits per 100 person-years in patients at increased risk decreased from 923 (95% CI, 901-944) before to 833 (95% CI, 696-969) after the SmPC changes. The rate in patients not at increased risk also decreased from 485 (95% CI, 473-497) before to 399 (95% CI, 331-468) after the SmPC changes. The RR comparing rates of visits between patients at increased risk and patients not at increased risk was 1.90 (95% CI, 1.84-1.97) in the period before the SmPC changes and 2.08 (95% CI, 1.65-2.64) in the period after the SmPC changes (Sweden, Table 19).

Reduction of Daily Dose in Patients Receiving Potentially Interacting Medications

The proportion of patients treated with interacting medications and cilostazol 200 mg per day at the start date was very similar in both periods, 58.4% before the SmPC changes and 57.0% after the SmPC changes. The proportion of patients concurrently treated with interacting medications and a daily dose of 200 mg during follow-up, decreased from 9.1% before to 6.7% after the SmPC changes (Sweden, Table 18). Reduction of the daily dose of 200 mg among patients concurrently treated with interacting medications was 0.4% (1 of 263 patients) before the SmPC changes and 0% (0 of 10 patients) after the SmPC changes.

For concurrent use of CYP3A4 or CYP2C19 potent inhibitors, at start date, approximately 1.0% of patients were concurrently treated with a daily dose of cilostazol 200 mg before and after the SmPC changes. During follow-up, 1.1% of patients before and no patients after the SmPC changes were concurrently treated with CYP3A4 or CYP2C19 potent inhibitors and a cilostazol daily dose of 200 mg (Sweden, Table 18B). The daily dose of 200 mg was not reduced in any of the patients concurrently treated with potent inhibitors before the SmPC changes.

Summary of the Evaluation of Changes to the Summary of Product Characteristics

A summary of the evaluation of the 2013 the SmPC changes is presented in Table 52. Compared to the period before the SmPC changes, the period after the SmPC changes was characterised by a slightly higher prevalence of smoking at the start date; an increase in the monitoring and early discontinuation of patients at the beginning of treatment; a lower prevalence of patients with the new cardiovascular contraindications in the period after the SmPC; a decrease in the concurrent use of cilostazol and two or

more platelet aggregation inhibitors; an increase in the monitoring of patients at high risk of severe cardiovascular events relative to the monitoring of patients at low risk; and a slight decrease in the concurrent use of a high daily dose of cilostazol and interacting medications, including CYP3A4 or CYP2C19 potent inhibitors.

Table 52. Overall Assessment of Variables Affected by the 2013 SmPC, Before and After the SmPC Changes; National Registers, Sweden

2013 Changes to the Summary of Product Characteristics	Study Variable	Before the SmPC Changes DUS 1 (N = 2,887) n (%) or Rate (95% CI)	After the SmPC Changes DUS 2 (N = 149) n (%) or Rate (95% CI)
Indication			
Second-line use after lifestyle modifications, including smoking cessation and (supervised) exercise programmes, failed to sufficiently improve symptoms	Current smoking at the start date	92 (3.2)	6 (4.0)
Physician reassessment of patients after 3 months of treatment with a view to discontinuing cilostazol if an inadequate effect is observed	▪ Visit to GP or specialist between 2 and 4 months after the start date	147 (8.6)	9 (13.0)
	▪ Visit related to intermittent claudication	146 (8.5)	9 (13.0)
	▪ Discontinuation before 3 months of treatment (cumulative proportion discontinuing)[a]	39.4	47.9
Contraindications			
Unstable angina pectoris, myocardial infarction within the last 6 months, or a coronary intervention in the last 6 months	As described in labelling	151 (5.2)	4 (2.7)
Concomitant treatment with two or more additional platelet aggregation inhibitors (e.g., aspirin, clopidogrel) at the start date and/or during follow-up	As described in labelling	243 (8.4)	6 (4.0)
Warnings and precautions			
Close monitoring of patients at increased risk for serious cardiac adverse events as a result of increased heart rate, e.g., patients with stable coronary disease or a history of tachyarrhythmias	Rate of visits to GP or specialist per 100 person-years		
	▪ No increased risk	485 (473-497)	399 (331-468)
	▪ Increased risk	923 (901-944)	833 (696-969)
	▪ RR increased/no increased risk	1.90 (1.84-1.97)	2.08 (1.65-2.64)
Posology			
Reduction of daily dose to 100 mg in patients receiving medicines interacting with CYP3A4 or CYP2C19 enzymes			

2013 Changes to the Summary of Product Characteristics	Study Variable	Before the SmPC Changes DUS 1 (N = 2,887) n (%) or Rate (95% CI)	After the SmPC Changes DUS 2 (N = 149) n (%) or Rate (95% CI)
Any interacting medication	Concurrent use of cilostazol 200 mg per day and interacting medications	1,950 (67.5)	95 (63.8)
	▪ At the start date	1,687 (58.4)	85 (57.0)
	▪ During follow-up	263 (9.1)	10 (6.7)
	Dose reduction after start of an interacting medication during follow-up	1 of 263 (0.4)	0 of 10
CYP3A4 or CYP2C19 potent inhibitors[b]	Concurrent use of cilostazol 200 mg per day and potent inhibitors	62 (2.1)	1 (0.7)
	▪ At the start date	30 (1.0)	1 (0.7)
	▪ During follow-up	32 (1.1)	0 (0.0)
	Dose reduction after start of a potent inhibitor during follow-up	0 of 32 (0.0)	NA (0 patients with a daily dose of 200 mg during follow-up)

CI = confidence interval; DUS = drug utilisation study; GP = general practitioner; NA = not applicable; RR = rate ratio; SmPC = summary of product characteristics.

[a] Cumulative proportion of patients discontinuing calculated using survival analysis.

[b] Potent CYP3A4 or CYP2C19 inhibitors: lansoprazole, fluvoxamine, nefazodone, ticlopidine, clarithromycin, troleandomycin, indinavir, ritonavir, nelfinavir, mibefradil, ketoconazole, and itraconazole.

10.4.4.6 Indication and Off-Label Use

See file Sweden_Results_Tables.xlsx, Table 21, for further detailed results.

The potential indication and off-label use of cilostazol was evaluated through diagnoses codes in both periods before and after the SmPC changes.

Results from the review are presented in Table 53. Potential off-label prescribing of cilostazol increased from 24.5% of users before to 34.2% after the SmPC changes. Musculoskeletal disorders were the most frequent potential off-label diagnoses in the period prior to the SmPC changes, and varices, phlebitis, and thrombophlebitis were the most frequent potential off-label diagnoses in the period after the SmPC changes.

Table 53. Indication and Potential Off-Label Prescribing of Cilostazol— Before and After the 2013 SmPC Changes; National Registers, Sweden

	Before the SmPC Changes DUS 1 (N = 2,887)		After the SmPC Changes DUS 2 (N = 149)	
Category and Diagnosis	Number of Users	Proportion	Number of Users	Proportion
On-label diagnosis[a]	2,026	70.2	81	54.4
Potential off-label diagnosis	706	24.5	51	34.2
Other cardiovascular diseases	469	16.2	32	21.5
Musculoskeletal disorders	108	3.7	5	3.4
Varices, phlebitis, thrombophlebitis	65	2.3	7	4.7
Leg/arm pain	38	1.3	5	3.4
Ischaemic heart disease	18	0.6	1	0.7
Cerebrovascular accident	8	0.3	1	0.7
No other diagnosis recorded	155	5.4	3	2.0

DUS = drug utilisation study; SmPC = summary of product characteristics.

[a] Diagnosis of intermittent claudication and/or peripheral arterial disease before the start date.

10.4.4.7 Hospitalisations

See file Sweden_Results_Tables.xlsx, Table 22, for detailed results.

The proportion of patients who had at least one hospitalisation during the period of continuous use of cilostazol decreased from 53.3% before to 46.3% after the SmPC changes.

10.5 Results, GePaRD, Germany

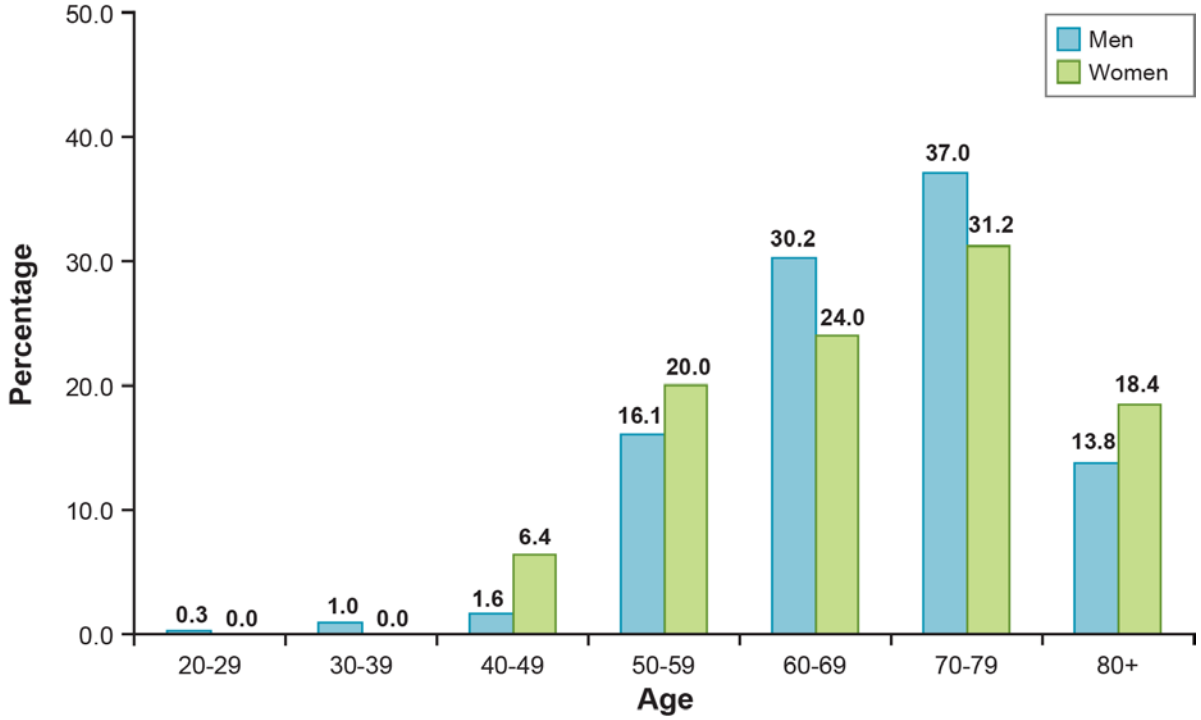
10.5.1 Participants

See file GePaRD_Results_Tables.xlsx, Tables 1, 4, 24, 25, and 31, for detailed results.

A total of 1,431 patients had a recorded prescription for cilostazol in 2014; of these, 436 (30.5%) were new users of cilostazol and were included in the DUS 2 analysis. Six of these new users (1.4%) had less than 12 months of enrolment in GePaRD before the start date.

The age and sex distribution of new users at the start date is presented in Figure 22. About 71% of new users were men. The median age was 70 years, 70 years for men and 69 years for women (GePaRD, Table 31); 50.8% of men and 49.6% of women were aged 70 years or older, and 13.8% of men and 18.4% of women were aged 80 years or older (GePaRD, Table 4).

Figure 22. Age and Sex Distribution of New Users of Cilostazol at the Start Date; GePaRD, Germany



GePaRD = German Pharmacoepidemiological Research Database.

The prevalence of use of cilostazol (new and prevalent users) in GePaRD in 2014 is presented in Table 54 (GePaRD, Table 25). The overall prevalence was 18.3 users per 100,000 population. Prevalence was higher in men (26.4 per 100,000 population) than in women (9.8 per 100,000 population) and increased by age, especially after 59 years of age in men and after 69 years of age in women. The highest prevalence was for the group aged 80+ years in both men and women.

Table 54. Age- and Sex-Specific Prevalence (per 100,000 Population) of Use of Cilostazol During the DUS 2 Study Period; GePaRD, Germany

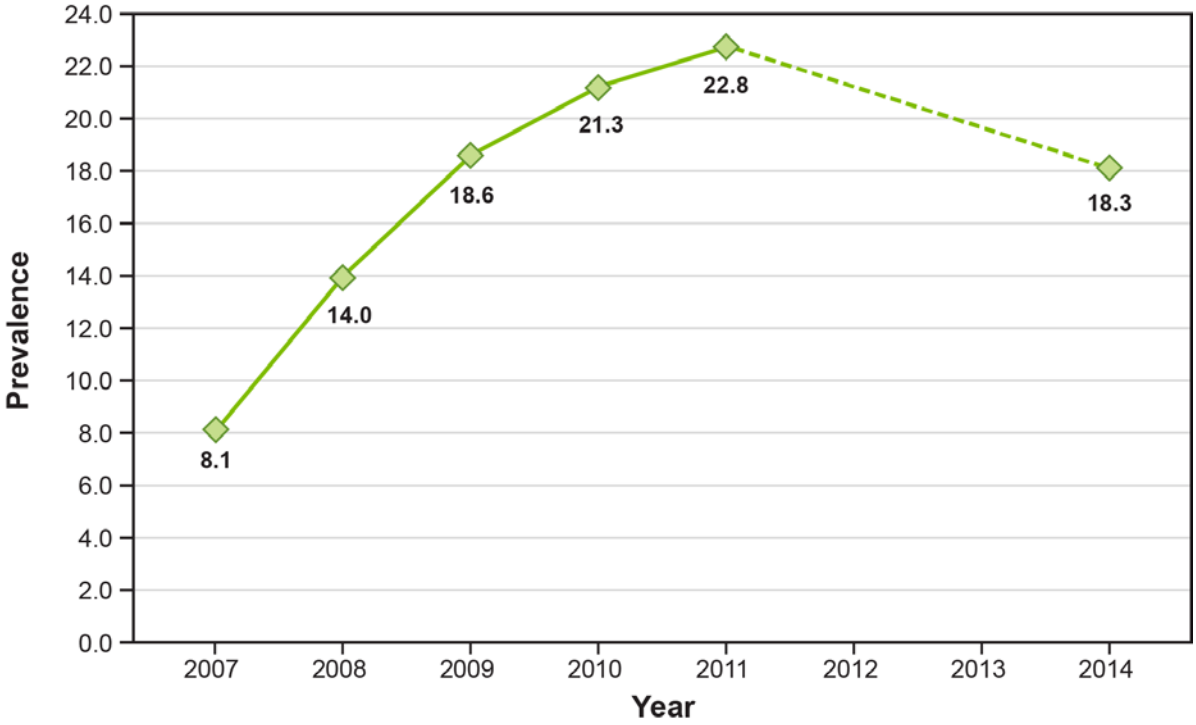
Age in Years	Men	Women	Total
20-29	0.5	0.0	0.2
30-39	1.3	0.2	0.8
40-49	2.8	3.7	3.2
50-59	23.8	8.6	16.4
60-69	72.2	27.1	52.2
70-79	106.9	43.6	79.2
80+	146.6	76.1	113.6
Total	26.4	9.8	18.3

DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database.

Note: Prevalence was calculated using the age and sex distribution of the population in GePaRD in 2014. The study period was from 1 January 2014 until 31 December 2014.

In Figure 23 and Table 55, we present the prevalence of use of cilostazol and the demographic characteristics of new users of cilostazol before (DUS 1) and after (DUS 2) implementation of the SmPC changes in 2013. The study period for DUS 1 was from 1 January 2007 to 31 December 2011, and the study period for DUS 2 was from 1 January 2014 to 31 December 2014. The prevalence of use in 2014, after the SmPC changes, was lower than in the three preceding years (2009 to 2011) contributing data to DUS 1 (Figure 23). The proportion of men, and the age distribution was similar for both periods, before and after the SmPC changes.

Figure 23. Annual Prevalence of Use of Cilostazol Before (2007-2011) and After (2014) the 2013 SmPC Changes; GePaRD, Germany



DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; SmPC = summary of product characteristics.

Note: Data for 2013 were not evaluated because that was the year the SmPC changes were implemented. Years from 2007 to 2011 correspond to the period before the SmPC changes (DUS 1), and the year 2014 corresponds to the period after the SmPC changes (DUS 2).

Table 55. Age and Sex Distribution of New Users of Cilostazol Before and After the 2013 SmPC Changes; GePaRD, Germany

Characteristic	Before the SmPC Changes DUS 1 (N = 4,012)	After the SmPC Changes DUS 2 (N = 430)
Study period	1 Jan 2007-31 Dec 2011	1 Jan 2014-31 Dec 2014
Number of new users	4,012	430
Men (%)	73.3%	70.9%
Median age (years)		
All	69.0	70.0
Men	69.0	70.0
Women	70.0	69.0
Age (years)		
> 60 (%)	78.8%	78.8%
> 70 men (%)	46.8%	50.8%
> 70 women (%)	51.6%	49.6%
> 80 men (%)	11.9%	13.8%
> 80 women (%)	19.9%	18.4%

DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; SmPC = summary of product characteristics.

10.5.2 Descriptive Data

See Section 10.1.4, Main Results.

10.5.3 Outcome Data

Not applicable.

10.5.4 Main Results

10.5.4.1 Utilisation Patterns

See file GePaRD_Results_Tables.xlsx, Tables 1 through 3, 5 through 7, 26, 29, and 30, for detailed results.

In Table 56, we present the utilisation patterns before and after implementation of the 2013 SmPC changes. The proportion of patients dispensed a single prescription of cilostazol increased from 32.9% before to 45.1% after the SmPC changes, and the proportion receiving five or more dispensings decreased from 38.0% to 13.9%. Prescribing of the 50-mg strength increased after the SmPC changes (14.5% before vs. 24.7% after) and decreased for the 100-mg strength (91.7% before vs. 84.0% after) (GePaRD, Table 1). The proportion of users receiving a daily dose of 100 mg increased after the SmPC changes (12.1% before vs. 23.0% after), while the proportion of users receiving a daily dose of 200 mg decreased after the SmPC changes (87.9% before vs. 77.0% after).

Table 56. Utilisation Patterns of Cilostazol Before and After the 2013 SmPC Changes; GePaRD, Germany

Drug Use Characteristic	Before the SmPC Changes DUS 1 (N = 4,012)	After the SmPC Changes DUS 2 (N = 430)
Total number of dispensings	11,295	1,054
Mean number of dispensings per user in study period	5.85	2.45
Total number of DDDs in study period	982,845.5	40,131
Mean number of DDDs per user in study period	244.98	93.33
Total number of dispensings per user in study period		
1	32.9%	45.1%
2-4	28.9%	41.0%
5+	38.0%	13.9%
Proportion of users dispensed 50-mg strength during the study period	14.5%	24.7%

Drug Use Characteristic	Before the SmPC Changes DUS 1 (N = 4,012)	After the SmPC Changes DUS 2 (N = 430)
Proportion of users dispensed 100-mg strength during the study period	91.7%	84.0%
Daily dose at the start date		
100 mg	12.1%	23.0%
200 mg	87.9%	77.0%

DDDs = defined daily doses (as defined by the World Health Organization); DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; SmPC = summary of product characteristics.

10.5.4.2 Characterisation of Users

See file GePaRD_Results_Tables.xlsx, Tables 8 and 9 for further detailed results.

The age and sex distribution of users of cilostazol has been described in Section 10.1.1.

The baseline comorbidity of users of cilostazol before and after the 2013 SmPC changes is presented in Table 57 (GePaRD, Table 8). In both periods, the most frequent conditions (> 20% of users) were cardiovascular disease, renal disease, COPD, skin disorders, diabetes mellitus, bleeding disorders, liver disease, malignancy, rheumatoid arthritis, and blood dyscrasias. Compared with before the SmPC changes, after the SmPC changes, a similar proportion of users had a history of cardiovascular disease (95.7% before vs. 95.3% after), diabetes mellitus (41.1% before vs. 39.1% after), liver disease and malignancy (approximately 25% in both periods), and peptic ulcer disease (8.8% in both periods). Prevalence of renal disease, COPD, skin disorders, bleeding disorders, rheumatoid arthritis, blood dyscrasias, asthma, and connective tissue disorders was higher after the SmPC changes.

Table 57. Baseline Comorbidity (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; GePaRD, Germany

Comorbidities	Before the SmPC Changes DUS 1 (N = 4,012)	After the SmPC Changes DUS 2 (N = 430)
Cardiovascular diseases[a]	95.7%	95.3%
Renal diseases	48.1%	55.8%
COPD	43.0%	55.3%
Skin disorders	42.1%	54.9 %
Diabetes mellitus	41.1%	39.1%
Bleeding disorders	27.9%	34.9%
Liver disease	25.4%	24.2%
Malignancy	25.0%	24.4%
Rheumatoid arthritis	23.0%	28.8%
Blood dyscrasias	23.0%	27.2%

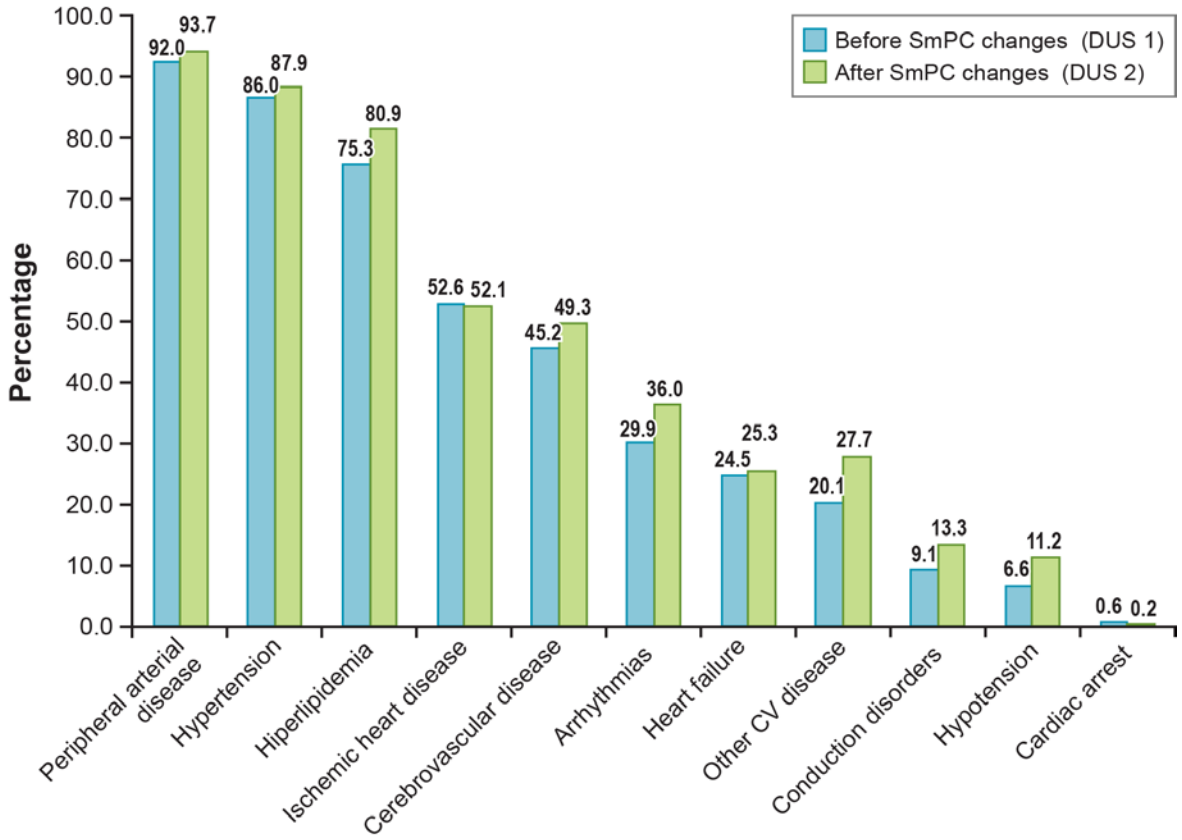
Comorbidities	Before the SmPC Changes DUS 1 (N = 4,012)	After the SmPC Changes DUS 2 (N = 430)
Asthma	9.8%	12.8%
Peptic ulcer disease	8.8%	8.8%
Connective tissue diseases	8.5%	14.7%
HIV	0.5%	1.4%

COPD = chronic obstructive pulmonary disease; DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; HIV = human immunodeficiency virus; SmPC = summary of product characteristics.

[a] Excluding diseases of arteries, arterioles, and capillaries.

The prevalence of cardiovascular conditions before and after the SmPC changes is presented in Figure 24. Peripheral arterial disease was the most frequent cardiovascular condition in both periods, before and after the SmPC changes (92.0% before vs. 93.7% after). Other conditions were similar in both periods: hypertension (86.0% before vs. 87.9% after), ischaemic heart disease (52.6% before vs. 52.1% after), and heart failure (24.5% before vs. 25.3% after). Hyperlipidaemia, cerebrovascular disease, arrhythmias, other cardiovascular diseases, conduction disorders, and hypotension were more frequent in the period after the SmPC changes.

Figure 24. Baseline Cardiovascular Comorbidity (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; GePaRD, Germany



CV = cardiovascular; DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; SmPC = summary of product characteristics.

The baseline use of comedications before and after the 2013 SmPC changes is presented in Table 58 (GePaRD, Table 9). The most frequent comedications (> 10% of users) in both periods were cardiovascular drugs, antithrombotics, musculoskeletal system drugs, drugs used in diabetes, proton pump inhibitors, respiratory medications, and antidepressants. After the SmPC changes, there was a higher proportion of users of proton pump inhibitors (25.0% before vs. 32.6% after), and a lower proportion of drugs used in diabetes (26.2% before vs. 20.0% after). The proportion of users of cardiovascular medications, antithrombotic agents, musculoskeletal system drugs, respiratory medications, and antidepressants was similar in both periods.

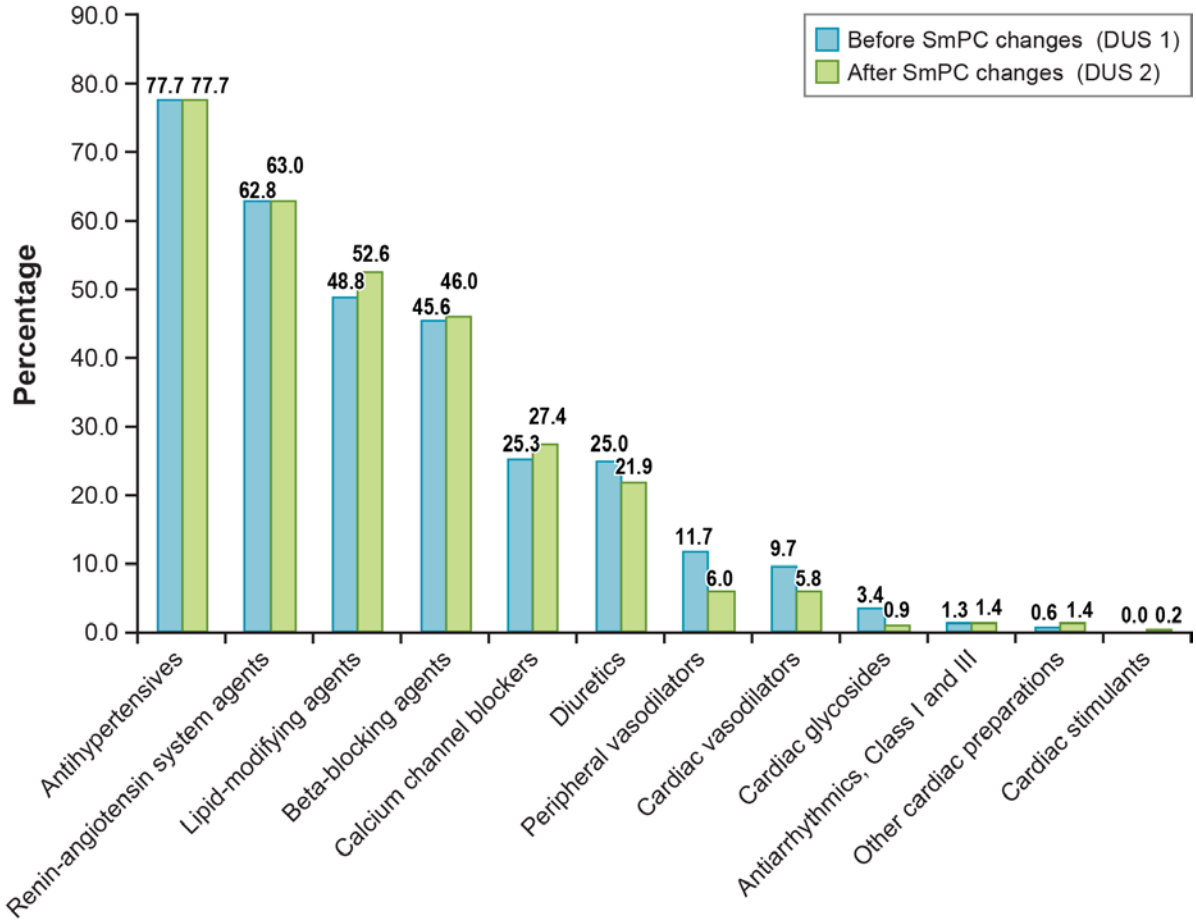
Table 58. Baseline Use of Comedications (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; GePaRD, Germany

Comedications	Before the SmPC Changes DUS 1 (N = 4,012)	After the SmPC Changes DUS 2 (N = 430)
Cardiovascular medications	85.5	85.3
Antithrombotic agents	44.1	44.7
Platelet aggregation inhibitors	33.8	34.4
Vitamin K antagonists	8.9	7.9
Heparins	8.2	7.2
Musculoskeletal system drugs	29.7	29.3
Drugs used in diabetes	26.2	20.0
Blood glucose–lowering drugs	18.6	13.7
Insulins	12.8	9.8
Proton pump inhibitors	25.0	32.6
Obstructive airway disease drugs	10.7	10.9
Antidepressants	9.9	11.9
Systemic corticosteroids	7.4	9.1
Hormone replacement therapy	2.8	3.7
Iron preparations	2.2	4.4
Immunosuppressants	1.1	1.4
Antivirals	0.8	1.4
Antineoplastic agents	0.7	0.0
Antinicotinics	0.0	0.0

DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; SmPC = summary of product characteristics.

The baseline use of cardiovascular medications before and after the SmPC changes is presented in Figure 25. Antihypertensives and renin-angiotensin system agents were the most frequent comedications before and after the 2013 SmPC changes. Other frequent cardiovascular medications were lipid-modifying agents, beta-blocking agents, calcium channel blockers, and diuretics.

Figure 25. Baseline Use of Cardiovascular Comedications (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; GePaRD, Germany



DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; SmPC = summary of product characteristics.

10.5.4.3 Concurrent Use of Potentially Interacting Medications

See file GePaRD_Results_Tables.xlsx, Tables 10 through 13 and 27 for further detailed results.

The concurrent use of potentially interacting comedications before and after the 2013 SmPC changes is presented in Table 59 (GePaRD, Table 13). The proportion of users concurrently treated with potentially interacting medications at the start date and/or during follow-up was similar in both periods.

The concurrent use of CYP3A4 and CYP2C19 potent inhibitors at the start date was similar for both periods, with 1.5% of users before and 1.6% of users after the SmPC changes. Concurrent use of CYP3A4 and CYP2C19 potent inhibitors at the start date and/or during continuous use of cilostazol was lower after the SmPC changes (3.8% before vs. 2.3% after) (Table 59).

Table 59. Concurrent Use of Potentially Interacting Medications (Proportion) Among New Users of Cilostazol Before and After the 2013 SmPC Changes; GePaRD, Germany

Potentially Interacting Medications	Before the SmPC Changes DUS 1 (N = 4,012)	After the SmPC Changes DUS 2 (N = 430)
Any interacting medication	78.8	81.4
Drugs interacting with CYP2C19	47.8	48.6
Substrates	47.5	48.6
Inhibitors	19.4	11.4
Drugs interacting with CYP3A4	66.0	70.7
Substrates	64.8	69.5
Inhibitors	7.6	4.4
Inducers	3.2	1.4
Potent inhibitors	3.8	2.3
CYP2C19 potent inhibitors	1.1	0.9
CYP3A4 potent inhibitors	2.7	1.4

DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; SmPC = summary of product characteristics.

Note: Potent CYP3A4 or CYP2C19 inhibitors were lansoprazole, fluvoxamine, nefazodone, ticlopidine, clarithromycin, troleandomycin, indinavir, ritonavir, nelfinavir, mibefradil, ketoconazole, and itraconazole.

The most frequently prescribed medications interacting with the CYP3A4 enzyme before and after the SmPC changes were simvastatin and amlodipine (Table 60), and the most frequently prescribed medications interacting with the CYP2C19 enzyme were clopidogrel, pantoprazole, and omeprazole (Table 61). After the SmPC changes, there was a higher proportion of users of pantoprazole (18.5% before vs. 25.6% after) and a lower proportion of users of omeprazole (17.2% before vs. 10.0% after).

Table 60. Concurrent Use of Cilostazol and Medications Interacting With the CYP3A4 Enzyme (Proportion), Before and After the 2013 SmPC Changes; GePaRD, Germany

Interacting Medication	Before the SmPC Changes DUS 1 (N = 4,012)	After the SmPC Changes DUS 2 (N = 430)
Simvastatin	48.9	41.2
Amlodipine	19.8	22.3
Verapamil	2.7	1.2
Clarithromycin	2.6	1.2
Nifedipine	2.4	2.3
Felodipine	1.7	0.7
Pioglitazone	1.5	0.0
Carbamazepine	1.4	0.7
Diazepam	1.3	0.9
Amiodarone	1.1	0.9

Interacting Medication	Before the SmPC Changes DUS 1 (N = 4,012)	After the SmPC Changes DUS 2 (N = 430)
Diltiazem	1.0	0.7
Atorvastatin	0.9	14.7[a]
Haloperidol	0.4	0.0
Alprazolam	0.3	0.7
Tacrolimus	0.3	0.5
Cyclosporine	0.2	0.2
Erythromycin	0.2	0.2
Tamoxifen	0.1	0.2
Triazolam	0.1	0.0
Methadone	0.0	0.2
Aripiprazole	0.0	0.0
Buspirone	0.0	0.0
Cisapride	0.0	0.0
Imatinib	0.0	0.0
Quinine	0.0	0.0
Phenytoin	0.0	0.0
Sildenafil	0.0	0.0

DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; SmPC = summary of product characteristics.

[a] Atorvastatin became available as a generic in 2012 in Germany.

Table 61. Concurrent Use of Cilostazol and Medications Interacting With the CYP2C19 Enzyme (Proportion), Before and After the 2013 SmPC Changes; GePaRD, Germany

Interacting Medication	Before the SmPC Changes DUS 1 (N = 4,012)	After the SmPC Changes DUS 2 (N = 430)
Clopidogrel	21.4	18.8
Pantoprazole	18.5	25.6
Omeprazole	17.2	10.0
Amitriptyline	3.3	4.7
Diazepam	1.3	0.9
Lansoprazole	0.8	0.9
Fluoxetine	0.4	0.0
Ticlopidine	0.2	0.0
Clomipramine	0.1	0.0
Ketoconazole	0.0	0.0
Phenytoin	0.0	0.0
Cyclophosphamide	0.0	0.0

DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; SmPC = summary of product characteristics.

The proportion of users concurrently treated with four or more interacting medications was decreased from 6.8% to 3.5% after the 2013 SmPC changes. The proportion of users treated with three interacting medications was 14.3% before and 15.8% after; two interacting medications, 25.5% and 30.2%; and a single interacting medication, 32.3% and 31.9% (GePaRD, Table 27).

10.5.4.4 Concurrent Use and Discontinuation of Antithrombotic Agents

See file GePaRD_Results_Tables.xlsx, Tables 14, 15, and 16, for further detailed results.

The proportion of users of cilostazol concurrently treated with antithrombotic agents at the start date and/or during follow-up decreased from 55.1% before to 50.2% after the SmPC changes. Concurrent use of cilostazol and platelet aggregation inhibitors was similar before (44.7%) and after (42.3%) the SmPC changes. The most frequently prescribed platelet aggregation inhibitors were acetylsalicylic acid (30.7% before vs. 29.1% after) and clopidogrel (21.0% before vs. 20.0% after) (GePaRD, Table 15).

Discontinuation of platelet aggregation inhibitors in the 60 days after the start of cilostazol decreased from 21.2% of cilostazol users before to 16.1% after the SmPC changes. In the sensitivity analysis, when the period to assess discontinuation of platelet aggregation inhibitors was reduced to 30 days, the discontinuation of platelet aggregation inhibitors decreased from 27.8% to 21.0%. When the period to assess discontinuation was extended to 90 days, the discontinuation of platelet aggregation inhibitors decreased from 16.2% to 12.9% (GePaRD, Table 16).

10.5.4.5 Evaluation of Changes to the Summary of Product Characteristics

See file GePaRD_Results_Tables.xlsx, Tables 17 through 20, for further detailed results.

In this section, we present the frequency of conditions included in the new cilostazol SmPC before and after implementation of the 2013 changes in the SmPC. Conditions evaluated were smoking status at the start date, monitoring of patients 3 months after initiating treatment, discontinuation of cilostazol, old and new contraindications, monitoring of patients at high risk of cardiovascular events, and reduction of daily dose from 200 mg to 100 mg in patients concurrently treated with interacting medications.

Smoking Status at the Start Date

Information on smoking was not available in the GePaRD database, and this variable was omitted from all analyses.

Monitoring of Patients After 3 Months to Evaluate Inadequate Effect of Cilostazol

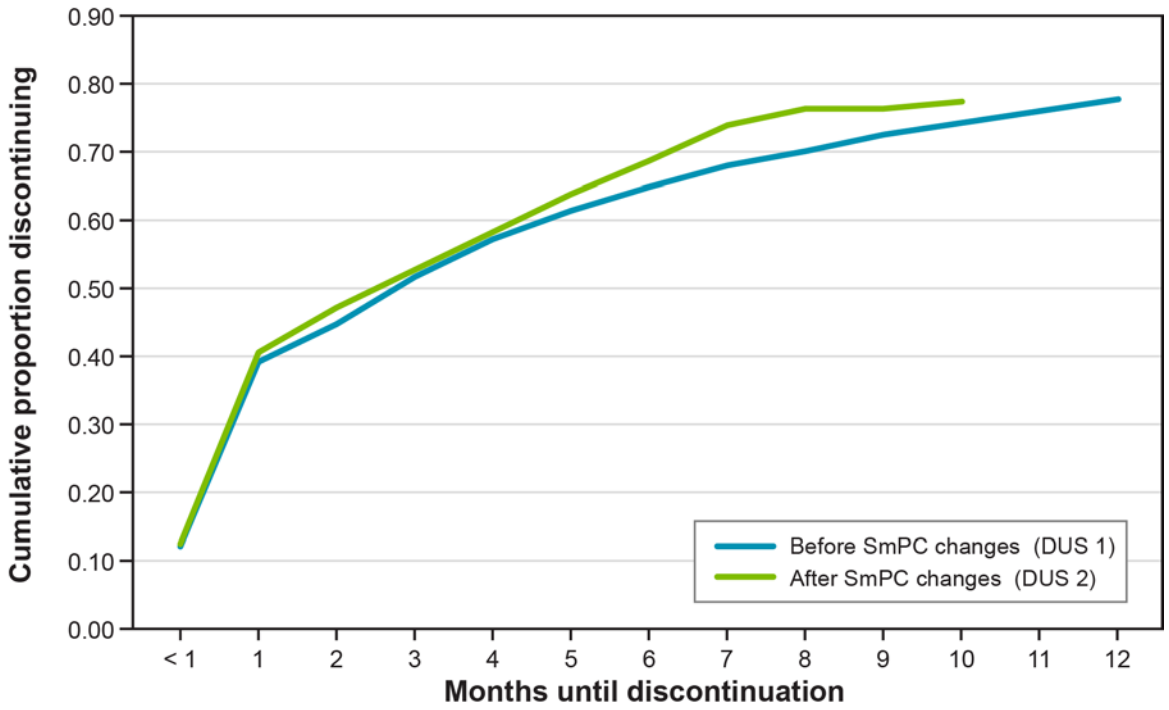
A total of 3,082 patients (76.8%) before the SmPC changes and 246 patients (57.2%) after the SmPC changes were users of cilostazol in the quarter following the quarter in which cilostazol was started. Among these patients, 62.2% before and 63.0% after the SmPC changes had a visit for intermittent claudication in this quarter, and 67.4% of

patients before and 67.5% after the SmPC changes had at least one visit for intermittent claudication within two quarters following the starting quarter (GePaRD Table 17BC).

Discontinuation of Cilostazol

Results from the survival analysis of the cumulative proportion of patients discontinuing cilostazol, by month, before and after the 2013 SmPC changes are presented in Figure 26 (GePaRD, Table 17A). By time since the start date, discontinuation of cilostazol was similar in both periods. The proportion of patients discontinuing before and after the SmPC changes was as follows: 39.4% vs. 40.7% in the first month, 51.9% vs. 52.8% in the first 3 months, 64.9% vs. 68.6% in the first 6 months, and 77.8% vs. 77.5% in the first 12 months.

Figure 26. Survival Analysis of Cilostazol Discontinuation Among New Users of Cilostazol Before and After the 2013 SmPC Changes, by Month; GePaRD, Germany



DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; SmPC = summary of product characteristics.

Contraindications

In Table 62, we present the number and proportion of users of cilostazol who had contraindications at the start of cilostazol treatment before and after the SmPC changes. Contraindications evaluated were those included in the labelling before the SmPC revision in 2013 (old contraindications) and those added in the labelling in the SmPC 2013 revision (new contraindications) (GePaRD Tables 17A, 20, 28).

The proportion of patients with old and new contraindications was similar before and after the SmPC changes. The proportion of users with old contraindications was 51.8% before and 54.7% after the SmPC changes, and the proportion with new

contraindications was 17.0% before and 18.1% after the SmPC changes. The proportion of users with new cardiovascular contraindications and concurrent use of cilostazol and two or more platelet aggregation inhibitors was similar in both periods.

Table 62. Contraindications Before and After the 2013 SmPC Changes; GePaRD, Germany

	Before the SmPC Changes DUS 1 (N = 4,012)		After the SmPC Changes DUS 2 (N = 430)	
Contraindication	**Number of Patients**	**Proportion**	**Number of Patients**	**Proportion**
Old contraindications (before 2013 SmPC revision)	**2,080**	**51.8**	**235**	**54.7**
Renal failure	830	20.7	116	27.0
Liver disease	1,021	25.4	104	24.2
Heart failure	155	3.9	17	4.0
Conditions predisposing to bleeding	655	16.3	69	16.0
Active peptic ulcer	155	3.9	15	3.5
Recent cerebral haemorrhage	26	0.6	1	0.2
Proliferative diabetic retinopathy	498	12.4	54	12.6
Poorly controlled hypertension	NA	NA	NA	NA
Arrhythmias	333	8.3	41	9.5
Ventricular tachycardia	62	1.5	5	1.2
Ventricular fibrillation or multifocal ventricular ectopics	294	7.3	39	9.1
Prolongation of the QT interval	NA	NA	NA	NA

Contraindication	Before the SmPC Changes DUS 1 (N = 4,012)		After the SmPC Changes DUS 2 (N = 430)	
	Number of Patients	Proportion	Number of Patients	Proportion
New contraindications (2013 SmPC revision)[a]	**683**	**17.0**	**78**	**18.1**
Cardiovascular diagnosis within 6 months before the start date	467	11.6	46	10.7
Myocardial infarction	386	9.6	39	9.1
Unstable angina	88	2.2	7	1.6
Coronary intervention	95	2.4	7	1.6
Concurrent use of cilostazol with two or more platelet aggregation inhibitors				
At the start date	160	4.0	19	4.4
At the start date and/or during continuous use of cilostazol	299	7.5	33	7.7
Any contraindication (old and new)	**2,332**	**58.1**	**261**	**60.7**

DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; NA = not applicable; SmPC = summary of product characteristics.

[a] New contraindications were added to labelling in addition to the old contraindications.

Monitoring of Patients at Increased Risk of Serious Cardiac Events

Because the number of medical visits is not recorded in GePaRD, monitoring of patients at increased risk of cardiovascular events was conducted using the number of quarters a patient had a diagnosis for intermittent claudication recorded during continuous use of cilostazol, expressed as rate per person per year. These rates were compared between users at increased risk of serious cardiac events and users not at increased risk. Increased risk was defined as a history of arrhythmias, coronary heart disease, or hypotension at any time before the start date.

Among the 4,012 new users of cilostazol included in DUS 1 (before the SmPC changes), 2,504 patients were at increased risk of serious cardiovascular events, and 1,508 patients were not at increased risk. The rate of quarters with a recorded diagnosis per person per year in patients at increased risk was 2.75 (95% CI, 2.68-2.82), and the rate in patients not at increased risk was 2.66 (95% CI, 2.58-2.75). The RR was 1.03 (95%

CI, 0.99-1.08). The RR was slightly higher in women (1.11, 95% CI, 1.02-1.21) than in men (1.01, 95% CI, 0.96-1.06) and was similar in both age groups (< 70 years and ≥ 70 years) (GePaRD, Table 19).

Among the 430 new users of cilostazol included in DUS 2 (after the SmPC changes), 281 patients were at increased risk of serious cardiovascular events, and 149 patients were not at increased risk. The rate of quarters with a recorded diagnosis per person per year in patients at increased risk was similar before (2.75; 95% CI, 2.68-2.82) and after (3.01; 95% CI, 2.63-3.42) the SmPC changes. The rate in patients not at increased risk also was similar before (2.66; 95% CI, 2.58-2.75) and after (2.42; 95% CI, 1.99-2.91) the SmPC changes. The RR comparing rates of visits between patients at increased risk and patients not at increased risk was 1.03 (95% CI, 0.99-1.08) in the period before the SmPC changes and 1.24 (95% CI, 0.99-1.56) in the period after the SmPC changes (GePaRD, Table 19).

Reduction of Daily Dose in Patients Receiving Potentially Interacting Medications

The proportion of patients treated with interacting medications and cilostazol 200 mg per day at the start date was similar in both periods, 57.3% before the SmPC changes and 54.4% after the SmPC changes. The proportion of patients concurrently treated with interacting medications and a daily dose of 200 mg during follow-up decreased from 12.1% before to 7.2% after the SmPC changes (GePaRD, Table 18). Reduction of the daily dose of 200 mg among patients concurrently treated with interacting medications was 0.2% (8 of 485 patients) before the SmPC changes and 3.2% (1 of 31 patients) after the SmPC changes.

Reduction of Daily Dose in Patients Receiving CYP3A4 or CYP2C19 Potent Inhibitors

The proportion of patients treated with CYP3A4 or CYP2C19 potent inhibitors and cilostazol 200 mg per day at the start date was similar before (1.5%) and after (1.2%) the SmPC changes. The proportion of patients concurrently treated with interacting medications and a daily dose of 200 mg during follow-up decreased from 2.1% before to 0.7% after the SmPC changes (GePaRD, Table 18). Reduction of the daily dose of 200 mg among patients concurrently treated with interacting medications during follow-up was 1.2% (1 of 85 patients) before the SmPC changes and 0% (0 of 3 patients) after the SmPC changes.

Summary of the Evaluation of Changes to the Summary of Product Characteristics

A summary of the evaluation of the 2013 the SmPC changes is presented in Table 63.

Most parameters evaluated in the new cilostazol labelling were similar before and after SmPC changes. There were no major changes in the monitoring and discontinuation of patients at the beginning of treatment, the prevalence of new cardiovascular contraindications, and the concurrent use of cilostazol and two or more platelet aggregation inhibitors. After SmPC changes, there was an increase in the monitoring of

patients at high risk of severe cardiovascular events relative to the monitoring of patients at low risk and a decrease in the concurrent use of a high daily dose of cilostazol and interacting medications, including CYP3A4 or CYP2C19 potent inhibitors.

Table 63. Overall Assessment of Variables Affected by the 2013 SmPC, Before and After the SmPC Changes; GePaRD, Germany

2013 Changes to the Summary of Product Characteristics	Study Variable	Before the SmPC Changes DUS 1 (N = 4,012) n (%) or Rate (95% CI)	After the SmPC Changes DUS 2 (N = 430) n (%) or Rate (95% CI)
Indication			
Second-line use after lifestyle modifications, including smoking cessation and (supervised) exercise programmes, failed to sufficiently improve symptoms	Current smoking at the start date	N/A	N/A
Physician reassessment of patients after 3 months of treatment with a view to discontinuing cilostazol if an inadequate effect is observed	▪ Visit to GP or specialist between 2 and 4 months after the start date	N/A	N/A
	▪ Visit related to intermittent claudication	1,917 (62.2)	155 (63.0)
	▪ Discontinuation before 3 months of treatment (cumulative proportion discontinuing)[a]	2,018 (50.3)	(227) 52.8%
Contraindications			
Unstable angina pectoris, myocardial infarction or a coronary intervention within the last 6 months	As described in labelling	467 (11.6)	46 (10.7)
Concomitant treatment with two or more additional platelet aggregation inhibitors (e.g., aspirin, clopidogrel) at the start date and/or during follow-up	As described in labelling	299 (7.5)	33 (7.7)
Warnings and precautions			
Close monitoring of patients at increased risk for serious cardiac adverse events as a result of increased heart rate, e.g., patients with stable coronary disease or a history of tachyarrhythmias	Rate of visits to GP or specialist per 100 person-years		
	▪ No increased risk	2.66 (95% CI, 2.58-2.75)	2.42 (1.99-2.91)
	▪ Increased risk	2.75 (95% CI, 2.68-2.82)	3.01 (2.63-3.42)
	▪ RR increased/no increased risk	1.03 (95% CI, 0.99-1.08)	1.24 (0.99-1.56)

2013 Changes to the Summary of Product Characteristics	Study Variable	Before the SmPC Changes DUS 1 (N = 4,012) n (%) or Rate (95% CI)	After the SmPC Changes DUS 2 (N = 430) n (%) or Rate (95% CI)
Posology			
Reduction of daily dose to 100 mg in patients receiving medicines interacting with CYP3A4 or CYP2C19 enzymes			
Any interacting medication	Concurrent use of cilostazol 200 mg per day and interacting medications	2,783 (69.4)	265 (61.6)
	▪ At the start date	2,298 (57.3)	234 (54.4)
	▪ During follow-up	485 (12.1)	31 (7.2)
	Dose reduction after start of an interacting medication during follow-up	8 (1.6)	1 (3.2)
CYP3A4 or CYP2C19 potent inhibitors[b]	Concurrent use of cilostazol 200 mg per day and potent inhibitors	144 (3.6)	8 (1.9)
	▪ At the start date	59 (1.5)	5 (1.2)
	▪ During follow-up	85 (2.1)	3 (0.7)
	Dose reduction after start of a potent inhibitor during follow-up	1 of 85 (1.2)	0 of 3 (0.0)

CI = confidence interval; DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; GP = general practitioner; N/A = not available; RR = rate ratio; SmPC = summary of product characteristics.

[a] Cumulative proportion of patients discontinuing cilostazol; calculated using survival analysis.

[b] Potent CYP3A4 or CYP2C19 inhibitors: lansoprazole, fluvoxamine, nefazodone, ticlopidine, clarithromycin, troleandomycin, indinavir, ritonavir, nelfinavir, mibefradil, ketoconazole, and itraconazole.

10.5.4.6 Indication and Off-Label Use

See file GePaRD_Results_Tables.xlsx, Table 21, for further detailed results.

The potential indication and off-label use of cilostazol was evaluated through diagnosis codes in both periods, before and after the SmPC changes.

Results from the review are presented in Table 64. Potential off-label prescribing of cilostazol increased from 17.0% of users before to 22.1% after the SmPC changes. Cardiovascular diseases other than ischaemic heart disease, cerebrovascular disease, hypertension, and peripheral arterial diseases were the most frequent potential off-label diagnoses before and after the SmPC changes.

Table 64. Indication and Potential Off-Label Prescribing of Cilostazol— Before and After the 2013 SmPC Changes; GePaRD, Germany

	Before the SmPC Changes DUS 1 (N = 4,012)		After the SmPC Changes DUS 2 (N = 430)	
Category and Diagnosis	**Number of Users**	**Proportion**	**Number of Users**	**Proportion**
On-label diagnosis[a]	3,272	81.6	335	77.9
Potential off-label diagnosis	681	17.0	95	22.1
Other cardiovascular diseases[b]	600	15.0	81	18.8
Musculoskeletal disorders	185	4.6	31	7.2
Varices, phlebitis, thrombophlebitis	156	3.9	20	4.7
Ischaemic heart disease	280	7.0	35	8.1
Cerebrovascular accident	191	4.8	25	5.8
No other diagnosis recorded	59	1.5	8	1.8

DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; SmPC = summary of product characteristics.

[a] Diagnosis of peripheral arterial disease before the start date.

[b] Cardiovascular diseases other than ischaemic heart disease, cerebrovascular disease, hypertension, and peripheral arterial diseases.

10.5.4.7 Hospitalisations

See file GePaRD_Results_Tables.xlsx, Table 22, for detailed results.

The proportion of patients who had at least one hospitalisation during the period of continuous use of cilostazol decreased from 36.1% before to 25.3% after the SmPC changes.

10.6 Summary of Results Across Countries and Databases

This section presents the main study results across the different study populations.

A total of 22,593 new users of cilostazol were included in the period before the SmPC changes (DUS 1), and 1,821 were included in the period after the SmPC changes (DUS 2) (Table 65). The EpiChron Cohort and SIDIAP, in Spain, contributed the largest number of users in both periods. The annual prevalence of use of cilostazol decreased in all databases. Prevalence per 100,000 population decreased from 11.8 (2010) to 9.9 (2014) in THIN, from 186.5 (2012) to 161.5 (2014) in EpiChron, from 150.8 (2011) to 64.7 (2014) in SIDIAP, from 16.5 (2010) to 7.2 (2014) in Sweden, and from 22.8 (2011) to 18.3 (2014) in GePaRD (Figure 27).

There was a higher proportion of men than women in all the study populations, ranging from 52.3% in Sweden to 77.3% in SIDIAP before the SmPC changes and from 58.4% in Sweden to 85.6% in EpiChron after the SmPC changes.

After the SmPC changes, the median of age decreased in IACS, SIDIAP, and Sweden and increased in THIN and GePaRD.

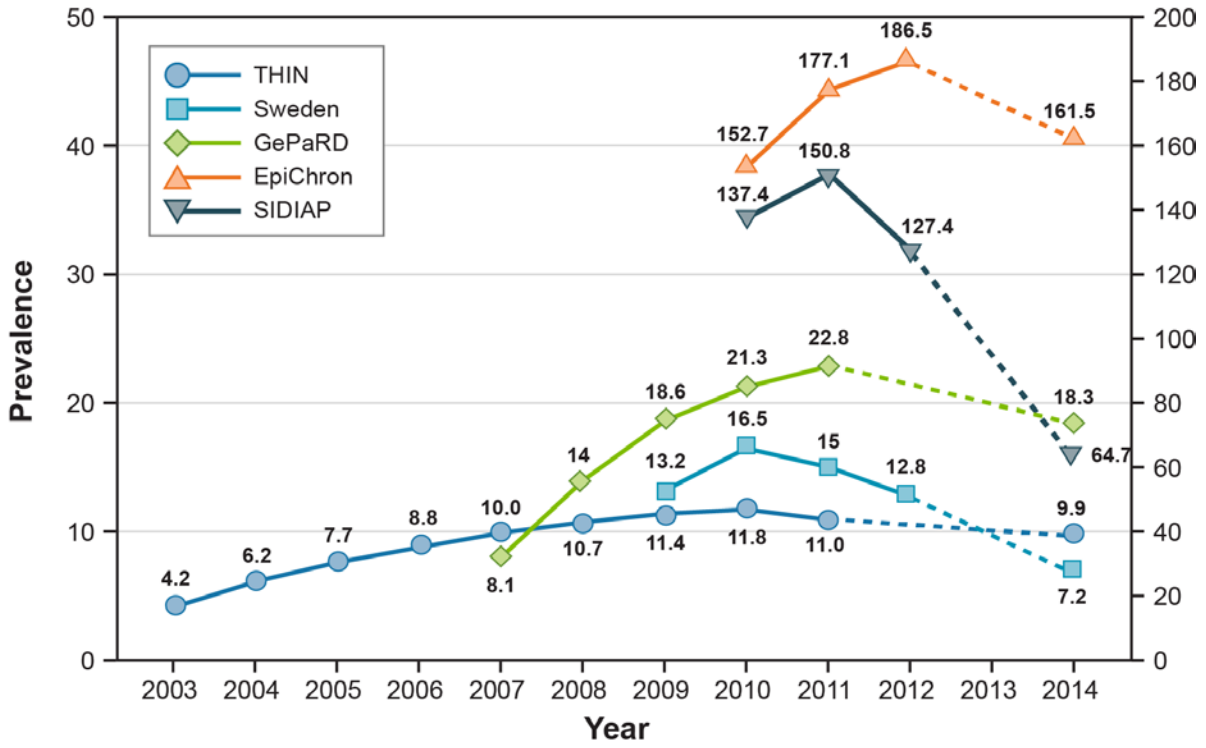
Table 65. Study Period, Number of Users, and Age and Sex Distribution of Users of Cilostazol

Characteristic	Study Period (SmPC Changes)	THIN, UK	EpiChron, Aragón, Spain	SIDIAP, Catalonia, Spain	Sweden	GePaRD, Germany
Study period	DUS 1	29 Jul 2002-14 Sep 2012	1 Jun 2009-31 Dec 2012	1 Jun 2009-31 Dec 2012	20 Mar 2008-31 Dec 2012	1 Jan 2007-31 Dec 2011
	DUS 2	1 Jan 2014-31 Dec 2014	1 Jan 2014-31 Dec 2014	1 Jan 2014-31 Dec 2014	1 Jan 2014-31 Dec 2014	1 Jan 2014-31 Dec 2014
Number of users	DUS 1	1,528	4,024	10,142	2,887	4,012
	DUS 2	104	367	771	149	430
Average annual prevalence of use (per 100,000)	DUS 1	8.9	162.4	133.5	13.3	17.0
	DUS 2	9.9	161.5	64.7	7.2	18.3
Men (%)	DUS 1	65.6%	72.2%	77.3%	52.3%	73.3%
	DUS 2	66.3%	85.6%	78.5%	58.4%	70.9%
Median age (years)						
All users	DUS 1	69.0	70.1	70.0	73.7	69.0
	DUS 2	71.0	66.3	65.0	71.0	70.0
Men	DUS 1	68.0	69.0	68.0	72.4	69.0
	DUS 2	69.0	65.9	65.0	69.7	70.0
Women	DUS 1	71.0	73.9	75.0	75.0	70.0
	DUS 2	74.0	69.7	68.0	72.5	69.0
Age (years)						
> 60 (%)	DUS 1	79.9%	77.5%	79.2%	90.0%	78.7%
	DUS 2	78.8%	71.7%	67.5%	84.6%	78.8%
> 70 men (%)	DUS 1	44.4%	46.9%	46.3%	58.7%	46.9%
	DUS 2	47.8%	34.7%	32.1%	49.4%	50.8%
> 70 women (%)	DUS 1	55.7%	58.5%	67.6%	68.9%	51.6%
	DUS 2	65.7%	49.1%	46.4%	66.1%	49.6%

Characteristic	Study Period (SmPC Changes)	THIN, UK	EpiChron, Aragón, Spain	SIDIAP, Catalonia, Spain	Sweden	GePaRD, Germany
> 80 men (%)	DUS 1	12.5%	16.5%	15.0%	22.5%	11.9%
	DUS 2	14.5%	8.9%	9.8%	24.1%	13.8%
> 80 women (%)	DUS 1	23.0%	25.7%	32.2%	31.2%	19.9%
	DUS 2	25.7%	18.9%	24.7%	24.2%	18.4%

DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; SIDIAP = Information System for the Improvement of Research in Primary Care database; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

Figure 27. Annual Prevalence of Use of Cilostazol Before (2003-2012) and After (2014) the 2013 SmPC Changes



GePaRD = German Pharmacoepidemiological Research Database; SIDIAP = Information System for the Improvement of Research in Primary Care database, Catalonia, Spain; SmPC = summary of product characteristics; THIN = The Health Improvement Network.

The patterns of use across the study populations are presented in Table 66. After the SmPC changes, the proportion of users of cilostazol 100 mg decreased in THIN, EpiChron, SIDIAP, and GePaRD and was practically the same as before the SmPC changes in Sweden.

The proportion of users of a daily dose of 200 mg at the start date decreased in THIN EpiChron, and GePaRD after the SmPC changes. In Sweden, the proportion of users of a daily dose of 200 mg was similar before and after the SmPC changes.

After the SmPC changes, discontinuation at 3 months and at 6 months increased in THIN, SIDIAP, and Sweden, decreased in EpiChron, and was practically the same as before the SmPC changes in GePaRD (Table 66).

Table 66. Patterns of Use of Cilostazol

Drug Use Characteristic	Study Period (SmPC Changes)	THIN, UK	EpiChron, Aragón, Spain	SIDIAP, Catalonia, Spain	Sweden	GePaRD, Germany
Number of users	DUS 1	1,528	4,024	10,142	2,887	4,012
	DUS 2	104	367	771	149	430
Users of 50 mg strength[a]	DUS 1	25.8%	NA	NA	23.4%	14.5%
	DUS 2	47.1%	33.5%	38.4%	21.5%	24.7%
Users of 100 mg strength	DUS 1	82.1%	100.0%	100.0%	81.0%	91.7%
	DUS 2	56.7%	73.8%	66.8%	80.5%	84.0%
Daily dose of 200 mg at start date (%)[b]	DUS 1	85.7%	77.3%	NA	78.1%	87.9%
	DUS 2	31.7%	7.1%	NA	79.9%	77.0%
Discontinuation of use						
< 1 month	DUS 1	28.7%	33.9%	22.2%	38.3%[c]	39.4%
	DUS 2	38.5%	25.5%	20.5%	43.0%	40.7%
< 3 months	DUS 1	52.9%	51.9%	40.6%	39.4%	51.9%
	DUS 2	64.4%	30.4%	58.1%	47.9%	52.8%
< 6 months	DUS 1	62.2%	60.5%	50.4%	65.2%	64.9%
	DUS 2	70.3%	35.2%	77.3%	70.6%	68.6%
< 12 months	DUS 1	71.3%	69.1%	64.6%	81.9%	77.8%
	DUS 2	70.3%	45.8%	100.0%	82.6%	77.5%

DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; NA = not applicable; SIDIAP = Information System for the Improvement of Research in Primary Care database; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

[a] Not available in Spain.

[b] Information on daily dose not available in SIDIAP.

[c] Refers to < 2 months.

Table 67 presents the most frequent baseline comorbidity affecting at least 10% of users in one database. In general, the pattern of comorbidity was similar before and after the SmPC changes, with some variations on the prevalence of specific conditions. Cardiovascular disease was the most frequent comorbidity in both periods, followed by diabetes, skin disorders, renal diseases, and bleeding disorders. Peripheral arterial disease, hypertension, and ischaemic heart disease were the most frequent cardiovascular diseases in both periods. After the SmPC changes, the prevalence of peripheral arterial disease decreased in THIN and Sweden, increased in EpiChron and SIDIAP, and was similar to the prevalence before the SmPC changes in GePaRD. It is important to keep in mind that in SIDIAP the recording of the ankle-brachial index started after 2012 in most primary care centres.

Table 67. Most Frequent Baseline Comorbidities (Proportion) by Database

Type of Comorbidity	Study Period (SmPC Changes)	THIN, UK	EpiChron, Aragón, Spain	SIDIAP, Catalonia, Spain	Sweden	GePaRD, Germany
Number of users	DUS 1	1,528	4,024	10,142	2,887	4,012
	DUS 2	104	367	771	149	430
Cardiovascular disease[a]						
	DUS 1	75.7	74.5	82.2	62.8	95.7
	DUS 2	76.0	57.8	83.9	63.8	95.3
Peripheral arterial disease						
	DUS 1	72.1	36.1	50.3	55.6	92.0
	DUS 2	64.4	48.8	79.2	38.9	93.7
Hypertension						
	DUS 1	54.0	54.9	63.0	46.8	86.0
	DUS 2	53.8	39.2	64.9	53.7	87.9
Ischaemic heart disease						
	DUS 1	32.5	14.0	17.2	31.6	52.6
	DUS 2	25.0	9.5	12.3	28.9	52.1
Hyperlipidaemia						
	DUS 1	31.3	37.4	48.5	20.4	75.3
	DUS 2	36.5	39.5	56.4	20.8	80.9
Skin disorders						
	DUS 1	26.1	15.9	8.7	7.8	42.1
	DUS 2	36.5	9.8	16.3	12.8	54.9
Renal disease						
	DUS 1	27.5	12.8	16.4	15.8	48.1
	DUS 2	31.7	5.2	25.8	15.4	55.8
Bleeding disorders						
	DUS 1	22.6	4.0	5.6	11.7	27.9
	DUS 2	30.8	3.3	9.7	15.4	34.9
Diabetes mellitus						
	DUS 1	21.3	29.9	40.4	20.5	41.1
	DUS 2	20.2	23.4	40.3	20.1	39.1

DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; SIDIAP = Information System for the Improvement of Research in Primary Care database; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

[a] Cardiovascular diseases: hypertension, ischaemic heart disease, hyperlipidaemia, cerebrovascular diseases, arrhythmias, heart failure, hypotension, conduction disorders, cardiac arrest, and other cardiovascular diseases. Excludes peripheral arterial disease.

The most frequent baseline comedications prescribed to at least 10% of users in each database are presented in Table 68. In general, the pattern of use of medications was similar before and after the SmPC changes. Antihypertensives, lipid-modifying agents, platelet aggregation inhibitors other than cilostazol, statins, and proton pump inhibitors were the most frequent comedications in both periods in all the study populations.

Table 68. Most Frequent Baseline Comedications (Proportion) by Database

Type of Comedication	Study Period (SmPC Changes)	THIN, UK	EpiChron, Aragón, Spain	SIDIAP, Catalonia, Spain	Sweden	GePaRD, Germany
Number of users	DUS 1	1,528	4,024	10,142	2,887	4,012
	DUS 2	104	367	771	149	430
Antihypertensives[a]						
	DUS 1	71.5	63.6	74.5	80.6	77.7
	DUS 2	65.4	64.3	68.5	70.5	77.7
Lipid-modifying agents[b]						
	DUS 1	68.6	45.8	63.6	61.6	48.8
	DUS 2	75.0	54.5	64.9	52.3	52.6
Platelet aggregation inhibitors[c]						
	DUS 1	67.3	46.9	73.1	69.7	33.8
	DUS 2	59.6	54.2	80.0	59.1	34.4
Statins						
	DUS 1	66.8	41.8	60.3	60.3	42.9
	DUS 2	73.1	49.6	62.4	51.7	49.3
Renin-angiotensin system agents						
	DUS 1	48.8	49.9	61.7	54.7	62.8
	DUS 2	47.1	55.3	58.5	51.0	63.0
Calcium channel blockers						
	DUS 1	34.5	18.6	23.6	37.8	25.3
	DUS 2	31.7	18.8	20.1	31.5	27.4
Diuretics						
	DUS 1	33.2	20.9	26.4	33.7	25.0
	DUS 2	24.0	15.5	21.1	21.5	21.9
Proton pump inhibitors						
	DUS 1	30.0	53.2	60.9	22.4	25.0
	DUS 2	49.0	50.7	49.7	26.2	32.6
Musculoskeletal system drugs						
	DUS 1	24.5	34.3	39.0	19.4	29.7
	DUS 2	14.4	29.4	19.8	12.1	29.3
Beta-blocking agents						
	DUS 1	22.2	14.7	18.4	44.1	45.6
	DUS 2	31.7	16.6	16.2	38.3	46.0
Peripheral vasodilators						
	DUS 1	12.5	33.6	37.7	0.3	11.7
	DUS 2	57.7	32.4	19.7	0.7	1.4

Type of Comedication	Study Period (SmPC Changes)	THIN, UK	EpiChron, Aragón, Spain	SIDIAP, Catalonia, Spain	Sweden	GePaRD, Germany
Blood glucose–lowering drugs						
	DUS 1	13.8	20.9	32.2	16.4	18.6
	DUS 2	10.6	26.7	31.9	16.1	13.7

DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; SIDIAP = Information System for the Improvement of Research in Primary Care database; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

[a] Antihypertensives: renin-angiotensin system agents, calcium channel blockers, diuretics, beta-blocking agents, and other antihypertensives (antiadrenergic agents, agents acting on arteriolar smooth muscle, antihypertensives and diuretics in combination, and other antihypertensives and combinations).

[b] Lipid-modifying agents: statins, fibrates, bile acid sequestrants, nicotinic acid and derivatives, and other lipid-modifying agents.

[c] Platelet aggregation inhibitors: excludes cilostazol.

The concurrent use of cilostazol and potentially interacting medications before and after SmPC changes is presented in Table 69. Most users in both periods were concurrently treated with interacting medications: from 78.8% (GePaRD) to 91.6% (THIN) before the SmPC changes and from 79.0% (EpiChron) to 91.3% (THIN) after the SmPC changes. The main change was in SIDIAP, with 90.0% before versus 84.7% after the SmPC changes.

The proportion of users of cilostazol concurrently treated with a CYP3A4 or CYP2C19 potent inhibitor at the start date or during follow-up decreased after the SmPC changes for all databases and ranged from 2.7% (Sweden) to 22.3% (THIN) before the SmPC changes and from 0.7% (Sweden) to 17.3% (THIN) after the SmPC changes.

Table 69. Concurrent Use (Proportion) of Most Frequent Potentially Interacting Medications

Potentially Interacting Medication	Study Period (SmPC Changes)	THIN, UK	EpiChron, Aragón, Spain	SIDIAP, Catalonia, Spain	Sweden	GePaRD, Germany
Number of users	DUS 1	1,528	4,024	10,142	2,887	4,012
	DUS 2	104	367	771	149	430
Any potentially interacting medication						
	DUS 1	91.6	82.5	90.0	84.4	78.8
	DUS 2	91.3	79.0	84.7	79.9	81.4
Any potent inhibitors of CYP3A4 or CYP2C19 enzymes						
	DUS 1	22.3	10.2	7.3	2.7	3.8
	DUS 2	17.3	3.0	2.1	0.7	2.3
Medications interacting with CYP3A4						
	DUS 1	85.3	57.2	73.2	78.2	66.0
	DUS 2	83.7	55.6	70.9	71.1	70.7
Simvastatin						
	DUS 1	44.0	17.6	38.0	55.7	48.9
	DUS 2	42.3	21.5	39.2	38.9	41.2
Atorvastatin						
	DUS 1	29.3	26.8	26.7	10.1	0.9
	DUS 2	26.0	24.8	24.5	23.5	14.7
Amlodipine						
	DUS 1	22.2	7.7	16.7	18.5	19.8
	DUS 2	13.5	7.6	15.4	21.5	22.3
Medications interacting with CYP2C19						
	DUS 1	55.3	71.7	75.3	37.4	47.8
	DUS 2	58.7	61.3	58.6	30.9	48.6
Omeprazole						
	DUS 1	22.4	47.7	59.3	23.6	17.2
	DUS 2	31.7	42.5	47.6	18.8	10.0
Clopidogrel						
	DUS 1	18.2	23.4	22.5	11.7	21.4
	DUS 2	11.5	17.2	11.2	7.4	18.8

DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; SIDIAP = Information System for the Improvement of Research in Primary Care database; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

Information on concurrent use of platelet aggregation inhibitors and discontinuation of these drugs is presented in Table 70. After the SmPC changes, concurrent use of cilostazol and platelet aggregation inhibitors decreased in THIN, Sweden, and GePaRD and increased in EpiChron and SIDIAP.

Discontinuation of platelet aggregation inhibitors during current use of cilostazol decreased after the SmPC changes in THIN, SIDIAP, and GePaRD and increased in EpiChron and Sweden.

Table 70. Concurrent Use (Proportion) of Platelet Aggregation Inhibitors and Discontinuation

Type of Use	Study Period (SmPC Changes)	THIN, UK	EpiChron, Aragón, Spain	SIDIAP, Catalonia, Spain	Sweden	GePaRD, Germany
Number of users	DUS 1	1,528	4,024	10,142	2,887	4,012
	DUS 2	104	367	771	149	430
Proportion of users of platelet aggregation inhibitors						
	DUS 1	76.4	62.3	62.9	74.3	44.7
	DUS 2	54.8	69.2	77.8	65.1	42.3
Proportion discontinuing platelet aggregation inhibitors						
	DUS 1	16.3	18.8	8.9	13.6	21.2
	DUS 2	6.7	60.0	6.3	18.4	16.1

DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; SIDIAP = Information System for the Improvement of Research in Primary Care database; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

The overall assessment of changes in the 2013 SmPC in each database is presented in Table 71. In the study databases with information from GPs (THIN, EpiChron, and SIDIAP), the prevalence of current smoking at the start date increased after the SmPC changes in THIN (30.4% before vs. 37.5% after) and in SIDIAP (32.3% before vs. 45.5% after), and decreased in EpiChron (15.9% before vs. 8.2% after). In Sweden, smoking at the start date was underestimated as it was evaluated through smoking-related diagnosis codes and dispensings for smoking-cessation drugs.

For databases with information from GPs, the proportion of patients with at least one visit with a GP and/or specialist between 2 months and 4 months after the start of cilostazol increased after the SmPC changes in THIN (80.9% before vs. 96.2% after), and decreased in EpiChron (83.6% before vs. 31.1% after) and SIDIAP (82.0% before vs. 13.6% after). The proportion of patients with at least one visit potentially related to intermittent claudication or peripheral arterial disease increased after the SmPC changes in THIN (49.6% before vs. 69.2% after) and EpiChron (21.3% before vs. 24.2% after), decreased in SIDIAP (53.5% before vs. 10.8% after), at was practically the same in both periods in GePaRD (62.2% before vs. 63.0% after).

Discontinuation of cilostazol within the first 3 months after the start of cilostazol increased after the SmPC changes in THIN (52.9% before vs. 64.4% after), SIDIAP (40.6% before vs. 58.1% after), and Sweden (39.4% before vs. 47.9% after),

decreased in EpiChron (51.9% before vs. 30.4% after), and was practically the same in both periods in GePaRD (50.3% before vs. 52.8% after).

The prevalence of new cardiovascular contraindications at the start date decreased after SmPC changes in THIN, EpiChron, SIDIAP, and Sweden, and was similar in both periods in GePaRD. After the SmPC changes, the concurrent use of cilostazol and two or more additional platelet aggregation inhibitors decreased in THIN (9.8% before vs. 3.8% after), EpiChron (13.5% before vs. 7.4% after), and Sweden (8.4% before vs. 6.7% after), and was approximately the same in both periods in SIDIAP and GePaRD.

In the period after the SmPC changes, the RR comparing the rates of visits with the GP and/or or specialists between users at increased risk of serious cardiac events and users without increased risk decreased in THIN and EpiChron, and increased in SIDIAP, Sweden, and GePaRD.

The proportion of users concurrently treated with cilostazol 200 mg per day and interacting medications decreased after the SmPC changes in all databases: from 78.7% to 27.9% in THIN, from 76.9% to 3.6% in EpiChron, from 67.5% to 63.8% in Sweden, and from 69.4% to 61.6% in GePaRD. After the SmPC changes, only 10 patients in Sweden and 31 in GePaRD were concurrently treated with a daily dose of 200 mg and interacting medications during follow-up. Only one of these patients (in GePaRD) had the daily dose reduced to less than 200 mg.

The proportion of users concurrently treated with cilostazol 200 mg per day and CYP3A4 or CYP2C19 potent inhibitors decreased after the SmPC changes in all databases: from 19.6% to 5.8% in THIN, from 10.0% to 0.0% in EpiChron, from 2.1% to 0.7% in Sweden, and from 3.6% to 1.9% in GePaRD. After the SmPC changes, there were no patients concurrently treated with a daily dose of 200 mg and interacting medications during follow-up.

Table 71. Overall Assessment of 2013 Summary of Product Characteristics Changes

2013 Changes to Summary of Product Characteristics		Study Variable	Study Period (SmPC Changes)	THIN, UK	EpiChron, Aragón, Spain	SIDIAP, Catalonia, Spain	Sweden	GePaRD, Germany
Number of users			DUS 1	1,528	4,024	10,142	2,887	4,012
			DUS 2	104	367	771	149	430
Restricted target population								
Indication	Second-line use after lifestyle modifications, including smoking cessation and (supervised) exercise programmes, failed to sufficiently improve symptoms	Current smoking at the start date						
			DUS 1	30.4%[a]	15.9%[a]	32.3%[a]	3.2%[b]	N/A
			DUS 2	37.5%	8.2%	45.5%	4.0%	N/A
	Physician reassessment of patients after 3 months of treatment with a view to discontinuing cilostazol if an inadequate effect is observed	Visit to GP or specialist between 2 and 4 months after the start date						
			DUS 1	80.9%	83.6%	82.0%	8.6%[c]	N/A
			DUS 2	96.2%	31.1%	13.6%	13.0%[c]	N/A
		Visit related to intermittent claudication						
			DUS 1	49.6%	21.3%	53.5%	8.5%[c]	62.2%
			DUS 2	69.2%	24.2%	10.8%	13.0%[c]	63.0%
		Discontinuation before 3 months of treatment						
			DUS 1	52.9%	51.9%	40.6%	39.4%	50.3%
			DUS 2	64.4%	30.4%	58.1%	47.9%	52.8%
Contra-indications	Unstable angina pectoris, myocardial infarction within the last 6 months, or a coronary intervention in the last 6 months	As described in labelling						
			DUS 1	1.5%	1.7%	3.0%	5.2%	11.6%
			DUS 2	1.0%	0.3%	0.9%	2.7%	10.7%
	Concomitant treatment with two or more additional antiplatelet agents (e.g., aspirin, clopidogrel)	As described in labelling						
			DUS 1	9.8%	13.5%	6.3%	8.4%	7.5%
			DUS 2	2.9%	7.4%	6.7%	6.7%	7.7%

2013 Changes to Summary of Product Characteristics		Study Variable	Study Period (SmPC Changes)	THIN, UK	EpiChron, Aragón, Spain	SIDIAP, Catalonia, Spain	Sweden	GePaRD, Germany
Other SmPC changes								
Warnings and precautions	Close monitoring of patients at increased risk for serious cardiac adverse events as a result of increased heart rate, e.g., patients with stable coronary disease or a history of tachyarrhythmias	Rate of visits to GP or specialist per 100 person-years (95% CI)						
		Increased risk (95% CI)						
			DUS 1	1,457 (1,430-1,485)	3,390 (3,348-3,432)	565 (556-575)	923[c] (901-944)	2.75 (2.68-2.82)[d]
			DUS 2	1,897 (1,567-2,275)	2,948 (2,747-3,160)	749 (705-796)	833 (696-969)[c]	3.01 (2.63-3.42)
		No increased risk (95% CI)						
			DUS 1	1,354 (1,335-1,373)	3,032 (3,013-3,052)	475 (470-480)	485[c] (473-497)	2.66 (2.58-2.75)[d]
			DUS 2	2,149 (1,933-2,381)	3,033 (2,955-3,112)	428 (412-445)	399 (331-468)	2.42 (1.99-2.91)
		RR for increased risk/ no increased risk (95% CI)						
			DUS 1	1.08 (1.05-1.10)	1.12 (1.10-1.13)	1.19 (1.17-1.22)	1.90 (1.84-1.97)	1.03 (0.99-1.08)
			DUS 2	0.88 (0.71-1.09)	0.97 (0.90-1.05)	1.75 (1.63-1.88)	2.08 (1.65-2.64)	1.24 (0.99-1.56)

2013 Changes to Summary of Product Characteristics		Study Variable	Study Period (SmPC Changes)	THIN, UK	EpiChron, Aragón, Spain	SIDIAP, Catalonia, Spain	Sweden	GePaRD, Germany
Posology	Reduction of daily dose to 100 mg in patients receiving medicines interacting with CYP3A4 or CYP2C19 enzymes							
	Any interaction medication	Concurrent use of cilostazol 200 mg per day and interacting medications						
			DUS 1	78.7%	76.9%	N/A	67.5%	69.4%
			DUS 2	27.9%	3.6%	N/A	63.8%	61.6%
		Dose reduction after start of an interacting medication during follow-up						
			DUS 1	0.0% (0 of 114)	0.9% (1 of 118)	N/A	0.4% (1 of 263)	1.6% (8 of 485)
			DUS 2	NA[e]	NA[e]	N/A	0.0% (0 of 10)	3.2% (1 of 31)
	CYP3A4 or CYP2C19 potent inhibitors[f]	Concurrent use of cilostazol 200 mg per day and potent inhibitors						
			DUS 1	19.6%	10.0%	N/A	2.1%	3.6%
			DUS 2	5.8%	0.0%	N/A	0.7%	1.9%
		Dose reduction after start of a potent inhibitor during follow-up						
			DUS 1	0.0% (0 of 148)	0.0% (0 of 33)	N/A	0.0% (0 of 32)	1.2% (1 of 85)
			DUS 2	NA[e]	NA[e]	N/A	NA[e]	0% (0 of 3)

CI = confidence interval; DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; GP = general practitioner; NA = not applicable; N/A = not available; RR = rate ratio; SIDIAP = Information System for the Improvement of Research in Primary Care database; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

[a] Smoking status in primary care.

[b] Smoking codes in hospital discharge codes, and smoking-cessation drugs.

[c] Based on hospital inpatient and outpatient visits only. Primary care visits were not available.

[d] Number of visits is not recorded in GePaRD. Rate refers to the number of quarters with a diagnosis related to intermittent claudication per patient-year recorded during continuous use of cilostazol.

[e] There were no patients concurrently treated with a daily dose of 200 mg and interacting medications.

[f] Potent CYP3A4 or CYP2C19 inhibitors: lansoprazole, fluvoxamine, nefazodone, ticlopidine, clarithromycin, troleandomycin, indinavir, ritonavir, nelfinavir, mibefradil, ketoconazole, and itraconazole.

The overall assessment of contraindications according to the labelling prior to the SmPC changes (old contraindications) and to the labelling after the SmPC changes (new contraindications) is presented in Table 72. After the SmPC changes, the proportion of users with old contraindications decreased in THIN (10.0% before vs. 8.7% after) and EpiChron (6.2% before vs. 5.5% after), increased in SIDIAP (39.1% before vs. 51.5% after) and GePaRD (51.8% before vs. 54.7% after), and was approximately 12% before and after the SmPC changes in Sweden. The proportion of users with new contraindications decreased from 10.7% to 3.8% in THIN, from 14.3% to 7.4% in EpiChron, from 8.7% to 6.7% in SIDIAP, and from 12.4% to 6.7% in Sweden and slightly increased from 17.0% to 18.1% in GePaRD. Overall, the proportion of users with old and/or new contraindications after the SmPC changes decreased in THIN (19.6% before vs. 11.5% after), EpiChron (19.4% before vs. 12.5% after), and Sweden (21.8% before vs. 18.8% after), and increased in SIDIAP (44.0% before vs. 55.1% after) and GePaRD (58.1% before vs. 60.7% after).

Table 72. Overall Assessment of Contraindications at the Start Date by Database

Contraindications	Study Period (SmPC Changes)	THIN, UK	EpiChron, Aragón, Spain	SIDIAP, Catalonia, Spain	Sweden	GePaRD, Germany
Number of users	DUS 1	1,528	4,024	10,142	2,887	4,012
	DUS 2	104	367	771	149	430
According to labelling prior to 2013 SmPC changes (old contra-indications)						
	DUS 1	10.0%[a]	6.2%[a]	39.1%	12.2%[a]	51.8%
	DUS 2	8.7%	5.5%	51.5%	12.1%	54.7%
According to new SmPC 2013 changes (new contraindications)						
	DUS 1	10.7%	14.3%	8.7%	12.4%	17.0%
	DUS 2	3.8%	7.4%	6.7%	6.7%	18.1%
Any contraindication (old and/or new contraindication)						
	DUS 1	19.6%[a]	19.4%[a]	44.0%	21.8%[a]	58.1%
	DUS 2	11.5%	12.5%	55.1%	18.8%	60.7%

DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; SIDIAP = Information System for the Improvement of Research in Primary Care database; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

[a] Poorly controlled hypertension could not be evaluated and was not included as contraindication.

Evaluation of potential off-label prescribing of cilostazol is presented in Table 73. After the SmPC changes, the proportion of users considered to have received cilostazol according to the product labelling decreased in THIN (93.4% before vs. 83.7% after), Sweden (70.2% before vs. 54.4% after), increased in EpiChron (53.6% before vs. 77.4% after) and SIDIAP (41.0% before vs. 79.2% after), and was approximately the same in GePaRD (81.6% before vs. 77.9% after). The proportion of users considered to have received cilostazol off-label ranged from 5.6% (THIN) to 24.5% (Sweden) before

the SmPC changes and from 0.8% (EpiChron) to 34.2% (Sweden) after the SmPC changes.

Table 73. Evaluation of Potential Off-Label Prescribing of Cilostazol

Diagnosis	Study Period (SmPC Changes)	THIN, UK[a]	EpiChron, Aragón, Spain[b]	SIDIAP, Catalonia, Spain[c]	Sweden[b]	GePaRD, Germany
Number of users	DUS 1	1,528	4,024	10,142	2,887	4,012
	DUS 2	104	367	771	149	430
On-label prescribing	DUS 1	93.4%	53.6%	41.0%	70.2%	81.6%
	DUS 2	83.7%	77.4%	79.2%	54.4%	77.9%
Potential off-label prescribing	DUS 1	5.6%	7.9%	10.3%	24.5%	17.0%
	DUS 2	9.6%	0.8%	6.4%	34.2%	22.1%
Varices, phlebitis, thrombophlebitis	DUS 1	0.0%	2.0%	2.1%	2.3%	3.9%
	DUS 2	0.0%	0.3%	0.0%	4.7%	4.7%
Leg and foot pain, symptoms, and complaints	DUS 1	3.6%	1.5%	2.1%	1.3%	0%
	DUS 2	7.7%	0.6%	0.0%	3.4%	0%
Musculoskeletal disorders	DUS 1	0.0%	1.2%	0.0%	3.7%	4.6%
	DUS 2	0.0%	0.0%	0.0%	3.4%	7.2%
Cerebrovascular disease	DUS 1	1.0%	0.3%	2.1%	0.3%	4.8%
	DUS 2	1.0%		2.9%	0.7%	5.8%
Ischaemic heart disease	DUS 1	0.5%	0.3%	1.0%	0.6%	7.0%
	DUS 2	1.0%	0.0%	2.7%	0.7%	8.1%
Other cardiovascular disease	DUS 1	0.0%	1.6%	0.0%	16.2%	15.0%
	DUS 2	0.0%	0.0%	1.8%	21.5%	18.8%
Peripheral neuritis, neuropathy	DUS 1	1.0%	0.02%	0.0%	0.0%	0%
	DUS 2	0.0%	0.0%	0.0%	0.0%	0%
Other diagnoses/no diagnoses recorded	DUS 1	1.0%	38.5%[c]	48.7%[d]	5.4%	1.5%
	DUS 2	6.7%	21.8%	14.4%	2.0%	1.8%

DUS = drug utilisation study; GePaRD = German Pharmacoepidemiological Research Database; SIDIAP = Information System for the Improvement of Research in Primary Care database; SmPC = summary of product characteristics; THIN = The Health Improvement Network; UK = United Kingdom.

[a] Based on clinical review of patient profiles and free text for a random sample of users in DUS 1, and for all patients in DUS 2.

[b] Based on recorded diagnosis and visit codes of all patients.

[c] Based on clinical review of patient profiles and free text of a random sample of users in DUS 1, and recorded diagnoses and visit codes of all patients in DUS 2.

10.7 Adverse Events/Adverse Reactions

Based on current guidelines from the International Society for Pharmacoepidemiology (2015, Section VI) and the EMA (2014, Section VI:C.1.2.1), noninterventional studies such as the one described in this protocol, conducted using medical record reviews or electronic claims and health care records, do not require expedited reporting of suspected adverse events/reactions. Given the type of data used for this study, no suspected adverse events/reactions were reported.

11 Discussion

11.1 Key Results

In this second DUS (DUS 2) conducted in THIN (UK), EpiChron (Spain), SIDIAP (Spain), Sweden, and GePaRD (Germany), we identified the characteristics of patients initiating cilostazol in the year 2014, after the SmPC changes were implemented, and compared them with the characteristics of patients initiating cilostazol in the period before implementation of the SmPC changes in 2013, which was the focus of DUS 1.

A total of 1,821 new users were included in DUS 2. The prevalence of use of cilostazol decreased in the last few years in all the study populations. After the SmPC changes, prescription of a daily dose of 200 mg decreased in THIN, EpiChron, and GePaRD and was practically the same as before the SmPC changes in Sweden. In general, the characteristics of new users of cilostazol were similar before and after implementation of the SmPC changes. In both periods, there was a higher proportion of men than women, and most users were elderly patients with a high prevalence of comorbidity, especially cardiovascular disease, and concurrent use of other medications.

The concurrent use of cilostazol and interacting medications decreased after the SmPC changes in EpiChron, SIDIAP, and Sweden, and was practically the same in both time periods in THIN and GePaRD. The concurrent use of cilostazol and CYP2C19 and CYP3A4 potent inhibitors decreased in all the study populations after the SmPC changes. Concurrent use of cilostazol and platelet aggregation inhibitors, and discontinuation of these agents after the start of cilostazol, decreased in THIN, Sweden, and GePaRD and increased in EpiChron and SIDIAP.

11.1.1 Evaluation of Changes to the Summary of Product Characteristics

In Table 74, we present a summary of the evaluation of changes to the SmPC after these were implemented in 2013. We assumed a 5% cut-off value for a positive or negative change comparing the period before and after SmPC changes. In general, compared with the period before the SmPC changes, the period after the SmPC changes was characterised by a higher prevalence of smoking at the start date, an increase in visits

related to the intermittent claudication at the beginning of treatment, an increase in the discontinuation of cilostazol in the first 3 months of treatment, a decrease in the prevalence of new cardiovascular contraindications, a decrease in the concurrent use of cilostazol and two or more platelet aggregation inhibitors, a decrease in the monitoring of patients at high risk of cardiac events in some populations and an increase in others, and a decrease in the concurrent use of a high daily dose of cilostazol and interacting medications, including CYP3A4 or CYP2C19 potent inhibitors.

Table 74. Before-and-After Evaluation of 2013 Summary of Product Characteristics Changes

Characteristic	THIN, UK	EpiChron, Aragón, Spain	SIDIAP, Catalonia, Spain	Sweden	GePaRD, Germany
Smoking at the start date	🔴	🟢	🔴	🔴	N/A
Visit related to intermittent claudication	🟢	🟢	🔴	🟢	🟠
Discontinuation before 3 months of treatment	🟢	🔴	🟢	🟢	🟢
New cardiovascular contraindications	🟢	🟢	🟢	🟢	🟢
Concomitant treatment with two or more additional antiplatelet agents	🟢	🟢	🔴	🟢	🟠
Monitoring of patients at high risk of cardiac events	🔴	🔴	🟢	🟢	🟢
Concurrent use of cilostazol 200 mg per day and interacting medications	🟢	🟢	N/A	🟢	🟢
Concurrent use of cilostazol 200 mg per day and potent inhibitors	🟢	🟢	N/A	🟢	🟢

GePaRD = German Pharmacoepidemiological Research Database; N/A = not available; SIDIAP = Information System for the Improvement of Research in Primary Care database; THIN = The Health Improvement Network; UK = United Kingdom.

Note: Classification is based on a 5% change before and after SmPC changes. Values below 5% are considered as no change. Green circle = improvement after the SmPC changes; Red circle = worsening after the SmPC changes; Orange circle = no changes after the SmPC changes.

11.1.2 Evaluation of Off-Label Prescribing of Cilostazol

After the SmPC changes, the proportion of users considered to have received cilostazol according to the product labelling decreased in THIN and Sweden, and increased in EpiChron, SIDIAP, and GePaRD.

11.2 Findings in Perspective With Other Studies

Published information on the use of cilostazol in general practice is scarce and limited to two drug utilisation studies conducted in Spain. One of these studies was conducted in the region of Cantabria by investigators from the regional health service and from the Spanish Medicines and Health Products Agency (SMHPA) (González-Ruíz et al., 2011). Results from the study were published in abstract format. The other study was conducted by the SMHPA using data from the BIFAP[1] database (Database for Pharmacoepidemiological Research in Primary Care) and included 2,316 new users of cilostazol. Partial results of this study were included in the Committee for Medicinal Products for Human Use (CHMP) referral assessment report for cilostazol (EMA data on file, 2012).

The results in our study, for both DUS 1 and DUS 2, are in line with results from these two prior studies in Spain. In both studies, most users of cilostazol were elderly and had a high prevalence of comorbidity and comedications. Results for DUS 2 indicate a decrease in the concurrent use of cilostazol and interacting medications, including CYP3A4 or CYP2C19 potent inhibitors.

In the BIFAP study, about 57% of users discontinued cilostazol in the first 6 months of treatment. This proportion is similar to that found in our study in the Spanish databases in DUS 1 (60.5% in EpiChron, and 50.4% in SIDIAP). However, in DUS 2 the proportion of users discontinuing in the first 6 months was lower in EpiChron (35.2%) and higher in SIDIAP (77.3%).

Not formal studies, but further information external to this study are sales data for cilostazol. The decrease in the prevalence of use found in this study is consistent with cilostazol sales data provided by Otsuka for the UK, Spain, Sweden, Germany, and Europe overall (Table 75). The number of units (tablets) of cilostazol sold in Europe decreased from approximately 47 million, between 1 March 2012 and 31 August 2012, to 15 million, between 31 August 2014 and 28 February 2015.

[1] Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP). BIFAP: A computerised database of medical records of primary care in Spain. Available at: http://www.bifap.org/summary.php. Accessed 23 August 2013.

Table 75. Number of Units (Tablets) of Cilostazol Sold in Europe, 6-Month Periods

Country	01 Mar 2012 to 31 Aug 2012[a]	01 Sep 2012 to 28 Feb 2013[b]	01 Mar 2013 to 30 Aug 2013[b]	31 Aug 2013 to 28 Feb 2014	01 Mar 2014 to 30 Aug 2014	31 Aug 2014 to 28 Feb 2015
United Kingdom	2,384,097	689,108	689,108	744,912	714,000	655,648
Spain	31,268,617	15,116,444	15,116,444	10,156,440	10,416,168	9,174,984
Sweden	213,869	40,964	40,964	29,596	26,558	28,322
Germany	9,750,106	4,240,460	4,240,460	2,991,170	2,995,034	2,222,556
Total for Europe	47,761,670	23,703,344	23,703,344	17,961,426	17,833,396	15,117,774

Note: Data provided by Otsuka, January 2017.

[a] Estimate based on taking 1/6 of the total for the entire 3-year period 2009-2012.

[b] Estimate based on taking 1/2 of the total for the entire 12-month period from 01 September 2012 to 30 August 2013.

11.3 Limitations

DUS 1 included a large number of users as the study periods covered several years in each database: from approximately 3.5 years in EpiChron and SIDIAP to 10 years in THIN. However, the study period for DUS 2 was restricted to new users identified during the year 2014. This resulted in the inclusion of a small number of users in all databases (from 104 in THIN to 771 in SIDIAP) and in a shorter time of follow-up, increasing random variability. A shorter time of follow-up could also result in underascertainment of those variables measured during continuous use of cilostazol in the follow-up period. Overall, random variability and a shortened time of follow-up in the period after SmPC changes should be taken into account when comparing the results of DUS 1 and DUS 2.

Changes in the recording of diagnoses in the study databases before and after the SmPC changes could affect the comparison of results between DUS 1 and DUS 2. For example, after the SmPC changes, the recording of the ankle-brachial index was implemented in SIDIAP, resulting in a higher prevalence of diagnoses. In addition, treatment guidances and introduction of new and generic medications in the period after SmPC changes also need to be considered. For example, direct oral anticoagulants were introduced recently in most countries; health services in Catalonia (SIDIAP) tried to reduce the consumption of proton pump inhibitors and encouraged general practitioners to review patient's prescriptions periodically; and atorvastatin became generic in Germany.

An advantage of using automated health databases is that they capture data from routine health care without interfering or modifying clinical practice and are a useful source of information for conducting drug utilisation and safety studies. The data recorded in the databases included in DUS 1 and DUS 2 allowed identification, characterisation, and comparison of a large number of users of cilostazol in several European populations. However, the use of automated health databases for research has

some limitations. Regarding prescription data, as is true for most databases, the study databases provide information on prescribed (THIN) or dispensed medications but not on the actual use of the medications by patients. Thus, patients may be classified as exposed when they are not actually taking the drug. However, information in EpiChron, SIDIAP, Sweden, and GePaRD was based on dispensed medications, which are more likely associated with actual use. Another limitation of databases is that they do not capture information on the use of over-the-counter medications, and we were not able to ascertain the concomitant use of cilostazol and relevant nonprescription medicines such as aspirin. For the THIN population, it is important to keep in mind that in the UK the first prescription may be written by a specialist and not captured in the Clinical Practice Research Datalink. However, continuing prescriptions are written by GPs for most medications. If a patient only received one prescription from a specialist, this patient will not have been included in our study.

Differences in the characteristics of the study databases may explain part of the baseline variability of the prevalence of comorbidity between databases in both DUS 1 and DUS 2. Information recorded in THIN, EpiChron, and SIDIAP is based on primary care electronic medical records; information recorded in Sweden is based on hospital discharge inpatient and hospital outpatient clinic diagnoses; and information recorded in GePaRD is based on insurance claims from ambulatory care visits and hospital admissions. SIDIAP and THIN also include hospital diagnoses. In SIDIAP, hospital diagnoses are recorded through linkage to the national hospital discharge codes database, and in THIN, hospital diagnoses are recorded by the GP, and recording may be incomplete. Therefore, the prevalence of comorbidity can be higher in those databases with more comprehensive information (SIDIAP, GePaRD, and THIN) than in those with more partial information as in EpiChron (primary care data) and Sweden (hospital data). These differences may also affect the evaluation of contraindications when these are assessed through recorded diagnoses. For example, the prevalence of prior history of renal failure and liver disease in DUS 1 was higher in GePaRD than in the other data sources.

The completeness of recording information may also differ between databases. Information on prescriptions and dispensings in the study databases can be considered to be complete in all databases, as it is based on an automatic recording of prescriptions or pharmacy dispensings. However, the recording of diagnoses may differ between physicians and databases. Data from THIN in the UK show that the recording of diagnoses is very good, since the prevalence of chronic and frequent disease estimated from information recorded in the database is similar to the prevalence estimated from national health statistics in the UK (Blak et al., 2011). Morbidity data from Sweden are based on the National Patient Register, which includes hospital discharge inpatient and outpatient diagnoses. The recording of these data can be considered to be very good, as the coding of diagnoses is required upon hospital discharge. However, prior history of many conditions will be underreported because the patients have not been hospitalised and data from nonhospital clinic ambulatory care are not available. Recording of data in

GePaRD can also be considered to be complete, as diagnoses are used for insurance billing purposes. The EpiChron and SIDIAP databases in Spain are based on information recorded by GPs, and the extent of recording can vary among physicians. In general, in this study, the prevalence of comorbidity was lower in EpiChron than in SIDIAP, although hospital discharge diagnoses were not available in EpiChron.

Potential off-label use was based on the absence of a recorded diagnosis and other clinical information compatible with intermittent claudication or peripheral arterial disease. However, the lack of recorded information does not exclude that the diagnosis may have occurred but may not have been recorded. This may have led to overestimation of potential off-label prescribing of cilostazol in the study populations.

11.4 Interpretation

In this DUS 2 conducted in THIN (UK), EpiChron (Spain), SIDIAP (Spain), Sweden, and Germany, we ascertained and compared the characteristics of new users of cilostazol in 2014 after implementation of the 2013 SmPC changes with the characteristics of new users before the SmPC changes (DUS 1). The study addressed the concerns raised during the EMA Article 31 cilostazol referral and the requirement to conduct a DUS in the EMA Rapporteur's Joint Assessment Report (July 2012) and the European Commission implementing decision (European Commission, 2013).

The prevalence of use of cilostazol decreased in all the study populations in the last few years. In both periods, before and after the SmPC changes, new users of cilostazol were mostly elderly men with a high prevalence of cardiovascular disease and concurrent use of other medications. In general, the results of this study are compatible with a positive effect of the labelling changes implemented in 2013, regarding the monitoring and early discontinuation of cilostazol, prevalence of new cardiovascular contraindications, concurrent use of two or more platelet aggregation inhibitors, and concomitant treatment of high-dose cilostazol and interacting drugs, including CYP2C19 and CYP3A4 potent inhibitors. However, labelling changes did not affect the prevalence of smoking at the start of treatment or the monitoring of patients at high cardiovascular risk in some of the study populations. These findings should be interpreted with caution given the random variation introduced by the small number of cilostazol users in DUS 2, the shorter time of follow-up after the 2013 SmPC changes, and the nature of the information recorded in each of the study data sources.

11.5 Generalisability

The THIN database includes information for approximately 6% of the UK population. The population covered in the database has been shown to have demographics, deprivation index, disease prevalence, and mortality rates similar to the overall UK population. Therefore, THIN is representative of the UK population, and results from this study can be generalised to UK patients treated with cilostazol (Blak et al., 2011).

Data included in EpiChron (Spain) correspond to the population of the region of Aragón covered by the primary health practices of the public health system.

SIDIAP (Spain) includes about 80% of the population in the region of Catalonia that is covered by public primary health practices.

In Sweden, data included in the study involve the entire population of Sweden.

In Germany, the four SHIs contributing data to GePaRD include about 20% of the German population. However, the population covered in this study is lower because it included data from two SHIs in DUS 1 and from one SHI in DUS 2. Overall, approximately 8.4 million insured members were covered in DUS 1, and 8.0 million insured members were covered in DUS 2.

Overall, the populations included in the study are representative of four European countries with diverse health systems.

12 Other Information

No complementary information was generated.

13 Conclusion

Results from this DUS 2 conducted in the UK, Spain, Sweden, and Germany are compatible with a decrease of the use of cilostazol and with a positive effect of the labelling changes implemented in 2013 regarding the monitoring and early discontinuation of cilostazol, prevalence of new cardiovascular contraindications, concurrent use of two or more platelet aggregation inhibitors, and concomitant treatment with high-dose cilostazol and interacting drugs, including CYP2C19 and CYP3A4 potent inhibitors. However, labelling changes did not affect the prevalence of smoking at the start of treatment or the monitoring of patients at high cardiovascular risk in some of the study populations. These findings should be interpreted with caution given the random variation introduced by the small number of cilostazol users in DUS 2, the shorter time of follow-up after the 2013 SmPC changes, and the nature of the information recorded in each of the study data sources.

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Appendices

Annex 1. List of Stand-Alone Documents

Number	Document Reference Number	Date	Title
1	THIN1	June 23, 2014	THIN Read Codes
2	THIN2	June 23, 2014	THIN Medication Codes
3	THIN3	February 2, 2017	DUS 2 THIN Results Tables
4	EpiChron	February 2, 2017	DUS 2 EpiChron Results Tables
5	SIDIAP	February 2, 2017	DUS 2 SIDIAP Results Tables
6	Sweden	February 2, 2017	DUS 2 Sweden Results Tables
7	GePaRD	February 2, 2017	DUS 2 GePaRD Results Tables

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