| | |
|---|---|
| *Study title* | **Drug utilisation study, in five European countries, using cross sectional analysis, to assess the extent of prescriptions of trimetazidine for its withdrawn ophthalmological and ENT indications among general practitioners, ophtalmologists and ENT specialists** |
| *Document title* | **Study protocol** |
| *Drug* | **Trimetazidine** |
| *Indication* | **Add-on therapy for the symptomatic treatment of adult patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapies** |
| *Development phase* | **Post-commercialization** |
| *Start of data collection* | **December 2012** |
| *End of data collection* | **July 2014** |
| *Location of databases* | **France, Spain, Poland, Greece, Romania** |
| *Company / sponsor* | **Les Laboratoires Servier** |
| *Subcontractor* | **IMS Health** |
| *Date of the document* | **2014-06-04 version 2** |
| | **CONFIDENTIAL** |

PROJECT TITLE:

***Drug utilisation study, in five European countries, using cross sectional analysis, to assess the extent of prescriptions of trimetazidine for its withdrawn ophthalmological and ENT indications among general practitioners, ophtalmologists and ENT specialists***

**Version 2**: June 4, 2014

IMS Health reference numbers: 903 600 - 903 601

PREPARED for:

SPONSOR

**Les Laboratoires Servier**
50 rue Carnot
92284 Suresnes - France

**Project team:**
**Mrs Sophie Perret**, European Regulatory Affairs Department Manager
E-mail: sophie.perret@fr.netgrs.com
**Mrs Karine Marinier**, Pharmacoepidemiology Project Manager
E-mail: karine.marinier@fr.netgrs.com
**Mr Nicolas Deltour**, Pharmacoepidemiology Department Director
E-mail: nicolas.deltour@fr.netgrs.com
**Mrs Catherine Regnier,** Marketing Evaluation Manager
E-mail: catherine.regnier@fr.netgrs.com

SUBCONTRACTOR:

**IMS Health**
Health Economics and Outcome Research (HEOR) department
Tour Ariane, 5-7, place des Pyramides
920888 La Défense cedex - France
**Project team:**

**Dr Massoud Toussi,** Medical director, HEOR, IMS Health France
E-mail: mtoussi@fr.imshealth.com, Phone number: +33 1 41 35 13 35

**Mrs Nathalie Grandfils,** Director of the databases studies, IMS HEOR, France
E-mail: ngrandfils@fr.imshealth.com

**Miss Isabelle Bardoulat,** Statistics manager, HEOR, IMS Health France
E-mail: ibardoulat@fr.imshealth.com

**Miss Anna Garofano**, Medical Writer, HEOR, IMS Health France
E-mail: agarofano@fr.imshealth.com

IMS is a partner centre of the ENCePP scientific network which is coordinated by the European Medicines Agency. IMS is dedicated to excellence in research by adhering to the ENCePP Guide on Methodological Standards and promoting scientific independence and transparency.

## Table of contents

## List of tables

## List of figures

## List of appendices

# 1. ABBREVIATIONS

| | |
|---|---|
| ATC | : Anatomical Therapeutic Chemical Classification System |
| CHMP | : Committee for Medicinal Products for Human Use |
| CI | : Confidence Interval |
| DHPC | : Direct Healthcare Professional Communication |
| DUS | : Drug Utilisation Study |
| EEA | : European Economic Area |
| EMA | : European Medicines Agency |
| ENT | : Ear Nose and Throat |
| EPPM | : Enquête Permanente sur la Prescription Medicale |
| EU | : European Union |
| GPs | : General Practitioners |
| HAS | : Haute Autorité de Santé |
| ICO | : International Classification of Diseases |
| IMS | : Intercontinental Marketing Services |
| ITS | : Interrupted Time Series |
| MAT | : Moving Annual Trend |
| NDI | : National Diagnostic Index |
| PI | : Prescribing Insights |
| PSUR | : Periodic Safety Update Report |
| RMP | : Risk Management Plan |
| SOP | : Standard Operating Procedure |
| STROBE | : Strengthening the Reporting of Observational Studies in Epidemiology |

## 2. TITLE OF THE DOCUMENT

Drug utilisation study, in five European countries, using cross sectional analysis, to assess the extent of prescriptions of trimetazidine for its withdrawn ophthalmological and ENT indications among general practitioners, ophtalmologists and ENT specialists.

## 3. MARKETING AUTHORISATION HOLDER

**Les Laboratoires Servier**
50 rue Carnot
92284 Suresnes – France

## 4. RESPONSIBLE PARTIES

**Sponsor: Les Laboratoires Servier**
*Project team:*
Mrs Sophie Perret, European Regulatory Affairs Department Manager
Mrs Karine Marinier, Pharmacoepidemiology Project Manager
Mr Nicolas Deltour, Pharmacoepidemiology Department Director
Mrs Catherine Regnier, Marketing Evaluation Manager

**Subcontractor: IMS Health France, HEOR department**
*Project team:*
Dr. Massoud Toussi, Medical Director
Mrs Nathalie Grandfils, Director of the Databases studies
Miss Isabelle Bardoulat, Statistics Manager
Miss Anna Garofano, Medical writer

## 5. ABSTRACT

***Title***
***Drug utilisation study, in five European countries, using cross sectional analysis, to assess the extent of prescriptions of trimetazidine for its withdrawn ophthalmological and ENT indications among general practitioners, ophtalmologists and ENT specialists***
First version submitted to EU member states (November 2012) and PRAC (July 2013)
Second version submitted to EMA and PRAC: June 2014
Main Author: Massoud Toussi, Medical Director, Real World Evidence Solutions, IMS Health.

***Rationale and background***
Further to the positive European re-evaluation of the Benefit/Risk of trimetazidine, adopted by the European Commission on September 3, 2012, the indication of trimetazidine was restricted to cardiology in adult patients "*as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by, or intolerant to, first-line antianginal therapies".*

The ophthalmological and ENT indications of trimetazidine were not maintained because its efficacy has not been considered sufficiently documented according to current guidelines and methodology.
The EMA recommended conducting the study using a cross-sectional analysis, among EU databases (database containing information collected at physician or pharmacy level) and performing the study among GPs, ENT specialists and ophthalmologists.

Following this referral, Les Laboratoires Servier committed to

- Send a DHPC letter to the concerned prescribers in order to communicate the outcome of the Committee for Medicinal Products for Human Use (CHMP) opinion in countries where trimetazidine was marketed,
- Perform a Drug Utilisation Study (DUS) to assess the extent of prescriptions of trimetazidine for its withdrawn ophthalmological and ENT indications among general practitioners, ophtalmologists and ENT specialits.

The present study protocol is in line with the synopsis of the Drug Utilisation Study, appended to the RMP agreed by the CHMP on June 21, 2012 and adopted by the EU commission on September 3, 2012 and has been updated according to the PRAC Rapporteur Assessment report dated February 2014. The study focuses on ophthalmological and ENT diagnoses of trimetazidine within the scope of its past indications.

The choice of the countries in which the study is going to be performed is based on the following:

- The countries where the ophthalmological and/or ENT indications were registered and marketed before the EU commission decision,
- The extent of patients exposure from market experience (using the last Periodic Safety Update Report (PSUR) data).

Taking into account this information, the study will be conducted in five countries: France, Greece, Poland, Romania and Spain which, taken together, represent 74% of the patient-exposure among the European countries.

***Research question and objectives***

Primary objective:

Assess, per country, the proportion of prescriptions of trimetazidine for ophthalmological or ENT diagnoses (within the scope of its past indications) among the total prescriptions of trimetazidine after the restriction of its indications.

Secondary objectives:

- Assess, per country, the extent of prescriptions of trimetazidine for ophthalmological or ENT diagnoses (within the scope of its past indications) by the GPs, ophthalmologists and ENT specialists before and after the restriction of its indications.
- Assess, per country, the extent of prescription of trimetazidine for ophthalmological or ENT diagnoses (within the scope of its past indications) with regards to GPs, ophthalmologists and ENT specialists' characteristics before and after the restriction of its indications.

- Illustrate, per country, the trends of prescription of trimetazidine for ophthalmological or ENT diagnoses (within the scope of its past indications) over time before and after its restriction of indications.
- Assess, per country, the extent of prescriptions of trimetazidine in the cardiovascular indication after the restriction of its indications.
- Assess, in countries where it is feasible (France and Spain), the extent of prescriptions of trimetazidine for angina pectoris without other concomitant prescriptions for angina pectoris after the restriction of its indications.

***Study design***
Cross-sectional study using prescription or delivery databases containing data collected by either GPs, ophthalmologists and ENT specialists (for France, Greece, Poland and Spain) or pharmacists (for Romania).

Two periods of data extraction will be studied:

- Reference period: one year period before the restriction of trimetazidine to cardiology (*i.e.* before the date of the CHMP positive opinion, June 21, 2012), from July 2011 to June 2012.
- Assessment period: a one year period beginning six months after sending of the DHPC letter to prescribers in countries where trimetazidine was marketed (*i.e.* after September / October 2012), from April 2013 to March 2014.

***Population***
The prescriptions of trimetazidine collected from patients who consulted GPs, ophthalmologists and ENT specialists during the study periods in the five targeted countries.
Eligible prescriptions are those containing trimetazidine, its brand or generic names.

***Variables***
The primary endpoint is the proportion of trimetazidine prescriptions for ophthalmological or ENT diagnoses (within the scope of its past indications) among all trimetazidine prescriptions made by the targeted prescribers of each country.
Information extracted from each database:

- Prescriber information: specialty, age, gender and region of practice within the country,
- Patient information: age, gender, date of the visit and place of visit,
- Prescription information: drug name, prescription date, ICD 10 codes and label of the diagnosis related to the prescription, prescription initiated or renew.

***Data sources***
Databases containing prescriptions made by the prescribers (GPs, Ophthalmologists and ENTs specialists) or the delivery of these prescriptions in pharmacy:

- IMS Prescribing Insights™ (PI) is available in France, Greece, Poland and Spain. It contains physicians' prescriptions and corresponding diagnoses and the prescribers' specialty.
- National Diagnostic Index™ (NDI) is available in Romania. It contains drug deliveries in pharmacy, the corresponding diagnoses and the prescribers' specialty.

***Study size***

The sample size calculation is based on the primary objective, *i.e*. the proportion of prescriptions of trimetazidine for ophthalmological and ENT diagnoses (within the scope of its past indications) among all prescriptions of this drug in each country. Since there is no evidence supporting the expected proportion after the restriction of its indications, the hypothetical proportion of those cases is considered as 50% (conservative assumption). For a confidence interval of 95% and an error margin of 5%, the required sample size would be 384 prescriptions for each country.

***Data analysis***

General statistical considerations:

The statistical analysis will be conducted using SAS® software Version 9.2 for Windows ™ (SAS Institute, North Carolina, USA).

Continuous variables will be described by the number of valid cases, the number of missing values, mean, standard deviation, median, Q1, Q3 and range.

Categorical variables will be described as the total number and relative percentage per category.

The number of missing data will be indicated. Missing data will not be taken into account for the calculation of the percentages.

Confidence intervals of 95% will be calculated for each item, when relevant.

The statistical unit will be the prescription (for extractions from PI database) or the dispensed prescription (for extractions from NDI database). Calculations will be performed on raw data.

Prescribers' profile will be described per country: age, gender and region.

Summaries will be reported at country level and by period (Reference period and assessment period) categorized according to the speciality.

Descriptive analysis:

- Primary endpoint:
  - Trimetazidine use will be evaluated using prescriptions or deliveries collected during the assessment period and expressed per country for GP's, ophthalmologists and ENT specialists. Two groups of trimetazidine prescriptions or deliveries will be identified according to the diagnosis: (a) ophthalmological diagnoses and (b) ENT diagnoses among (c) the total of diagnoses. use of trimetazidine in its past ophthalmological and ENT will be calculated as: (a+b)/c.
- Secondary end points:
  - Extent of prescriptions or deliveries of trimetazidine for the ophthalmological or ENT diagnoses by GPs, ophthalmologists and ENT specialists before and after the restriction of its indications. The distribution of trimetazidine use in its past indications will be expressed across specialties per country.
  - Extent of prescriptions or deliveries of trimetazidine for the ophthalmological or ENT diagnoses by specialist' characteristics before and after the restriction of indications.
  - Trends of prescriptions or deliveries of trimetazidine for the ophthalmological or ENT diagnoses over time before and after its restriction of indications.
  - To study the evolution of physicians' prescribing behaviour over time, the proportions of ophthalmological or ENT diagnoses will be refined by semester.
  - Extend of prescriptions of trimetazidine by GPs in the cardiovascular indication after its restriction of indications (only in IMS PI).

- Extend of prescriptions of trimetazidine by GPs for angina pectoris without other concomitant prescriptions for angina pectoris after its restriction of indications (only in France and Spain)

***Milestones***
Start of data collection : December 2012
End of data collection : July 2014
Final report of study results : September 2014

## 6. AMENDMENTS AND UPDATES

| Number | Date | Section of study protocol | Amendment or update | Reason |
|---|---|---|---|---|
| V2 | 04 June 2014 | 4. Responsible parties | One additional name for Sponsor Team | PRAC assessment report |
| | | 5. Abstract | Updated accordingly | |
| | | 9. Objectives of the study | Additional secondary objectives | |
| | | 10.3 Variables | Secondary endpoints added<br>ICD10 cardiovascular diagnoses added | |
| | | 10.4 Data sources | Additional description (classification system, data collection, coding, validation and quality control) | |
| | | 10.5 Study size | Possibility for the extension of data collection periods | |
| | | 10.7.3 Descriptive analysis | Conditions for the ITS design<br>Additional analyses on secondary endpoints | |
| | | 10.9 Limitations | Definition of cardiovascular diagnoses<br>Definition of concomitant medication<br>Panel composition and representativeness | |
| | | 15. Appendices | Appendices 6 and 7 added | |

## 7. MILESTONES

Start of data collection : December 2012
End of data collection : July 2014
Final report of study results : September 2014

# 8. BACKGROUND AND RATIONALE FOR COUNTRY SELECTION

## 8.1. Background

Further to the positive European re-evaluation of the Benefit/Risk of medicinal products containing trimetazidine (referral under article 31 of Directive 2001/83/EC), adopted by the European Commission on September 3, 2012, the indication of trimetazidine was restricted to cardiology in adult patients *"as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by, or intolerant to, first-line antianginal therapies"*(1).

The ophthalmological and ENT indications were not maintained because the efficacy of trimetazidine has not been considered sufficiently documented according to current guidelines and methodology.

In the frame of this referral, Les Laboratoires Servier committed to:

- Send a DHPC letter to the concerned prescribers to communicate the Committee for Medicinal Products for Human Use (CHMP) opinion in countries where trimetazidine was marketed, within 25 days after the adoption by the European Commission,
- Perform a Drug Utilisation Study to assess the extent of prescriptions of trimetazidine for its withdrawn ophthalmological and ENT indications among general practitioners, ophtalmologists and ENT specialists.

The present study protocol is in line with the synopsis of the Drug Utilisation Study, appended to the RMP agreed by the CHMP on June 21, 2012, adopted by the EU Commission on September 3, 2012 and has been updated according to the PRAC Rapporteur Assessment report dated February 2014. The study focuses on ophthalmological and ENT diagnoses of trimetazidine within the scope of its past indications.

In addition, during the evaluation process, the EMA recommended the following regarding the Drug Utilisation Study:

- To conduct the study using a cross-sectional analysis,
- To use EU databases (including database to collect information at physician or pharmacy level),
- To perform the study in GPs, ENTs and ophthalmologist specialists.

## 8.2. Rationale for country selection

The choice of the countries in which the study is going to be performed is based on the following:

1. Whether the ophthalmological and/or ENT indications were registered and marketed in the countries before the EU commission decision, *i.e.*:
    - Countries in which the three indications were registered and marketed: France, Greece, Romania, Cyprus, Ireland, Luxembourg and Malta.
    - Countries in which two indications (cardiology and ENT) were registered and marketed: Spain, Poland, Bulgaria and Hungary,
    - Countries in which one indication (ENT) was registered: Denmark.

2. The extent of patients exposure from market experience for the above mentioned countries taking into account the data from the last Periodic Safety Update Report (PSUR) that covered the period from February 2009 to January 2012 (see Table (8.2) 1).
3. Overall, the countries in which the product was the most marketed were: France, Greece, Poland, Romania and Spain.
4. Availability of EU databases to retrieve the information. All the countries listed in point two above were eligible.

Consequently, the study will be conducted in five countries: France, Greece, Poland, Romania and Spain. These five countries represent 74% of the patient-exposure among the European countries.

**Table (8.2) 1 - Patient exposure from marketed experience - EEA Countries**
**Source: PSUR period from 01/02/2009 to 31/01/2012**

| Countries | Market Authorisation | Number of patient-months | |
|---|---|---|---|
| | | Since Market Authorisation until 31-JAN-2012 | PSUR period from 01-FEB-2009 to 31-JAN-2012 |
| France* | Oct 1980 | 228 900 885 | 23 429 628 |
| Luxemburg | Apr 1982 | 389 505 | 21 163 |
| Portugal | Dec 1984 | 27 100 204 | 5 736 814 |
| Greece | Jan 1986 | 20 806 334 | 4 390 038 |
| Spain | Mar 1986 | 29 937 957 | 4 820 388 |
| Ireland | Oct 1987 | 589 264 | 39 441 |
| Cyprus | 1988 | 460 464 | 156 552 |
| Malta | Sep 1991 | 225 052 | 95 527 |
| Romania | Sep 1991 | 20 780 495 | 9 547 185 |
| Poland | Oct 1994 | 20 228 672 | 4 707 068 |
| Italy | May 1995 | 1 691 657 | 230 846 |
| Denmark | Feb 1996 | 114 228 | 24 244 |
| Latvia | Jan 1997 | 902 097 | 292 766 |
| Bulgaria | May 1997 | 5 837 481 | 1 859 526 |
| Lithuania | May 1997 | 2 169 919 | 1 130 135 |
| Czech Republic | Sep 1997 | 4 610 629 | 1 740 553 |
| Slovakia | Sep 1997 | 6 376 879 | 2 034 142 |
| Hungary | Dec 1997 | 20 745 130 | 4 156 287 |
| Slovenia | Jan1999 | 277 525 | 178 169 |
| Estonie | Nov 2002 | 504 359 | 248 447 |
| **EU countries** | | **392 684 736** | **63 251 308** |

** Including Guadeloupe, Guiana, Martinique, Reunion and Mayotta.*

This study protocol is in line with the synopsis of the Drug Utilisation Study, appended to the RMP that was agreed by the CHMP on June 21, 2012, and adopted by the European Commission on September 3, 2012.

# 9. OBJECTIVES OF THE STUDY

The aim of this study is to assess the extent of prescriptions of trimetazidine for its withdrawn ophthalmological and ENT indications among general practitioners, ophthalmologists and ENT specialists in five EU countries (France, Greece, Poland, Romania and Spain).

The primary objective is to:

- Assess, per country, the proportion of prescriptions of trimetazidine for ophthalmological or ENT diagnoses (within the scope of its past indications) among the total prescriptions of trimetazidine after the restriction of its indications.

Secondary objectives are to:

- Assess, per country, the extent of prescriptions of trimetazidine for ophthalmological or ENT diagnoses (within the scope of its past indications) by GPs, ophthalmologists and ENT specialists before and after the restriction of its indications.
- Assess, per country, the extent of prescriptions of trimetazidine for ophthalmological or ENT diagnoses (within the scope of its past indications) with regards to specialists' characteristics (see Section 10.7.1) before and after the restriction of its indications.
- Illustrate, per country, the trends of prescription of trimetazidine for ophthalmological or ENT diagnoses (within the scope of its past indications) over time before and after its restriction of indications.
- Assess, per country, the extent of prescriptions of trimetazidine by GPs[1] in the cardiovascular indication after the restriction of its indications.
- Assess, in countries where it is feasible (France and Spain), the extent of prescriptions of trimetazidine by GPs[1] for angina pectoris without other concomitant prescriptions for angina pectoris after the restriction of its indications.

# 10. RESEARCH METHODS

## 10.1. Study design

Cross-sectional and non-interventional study using prescription or delivery databases (secondary use of data already collected by GPs, ophthalmologists and ENT specialists, or pharmacists) in each participating country.

## 10.2. Setting

The study is conducted on prescription/delivery databases during the study period in all of the participating countries (France, Greece, Poland, Romania and Spain).

Two periods of data extraction, one before (reference period) and another one after the restriction of trimetazidine indications to cardiology (assessment period), will be studied taking into account the following considerations:

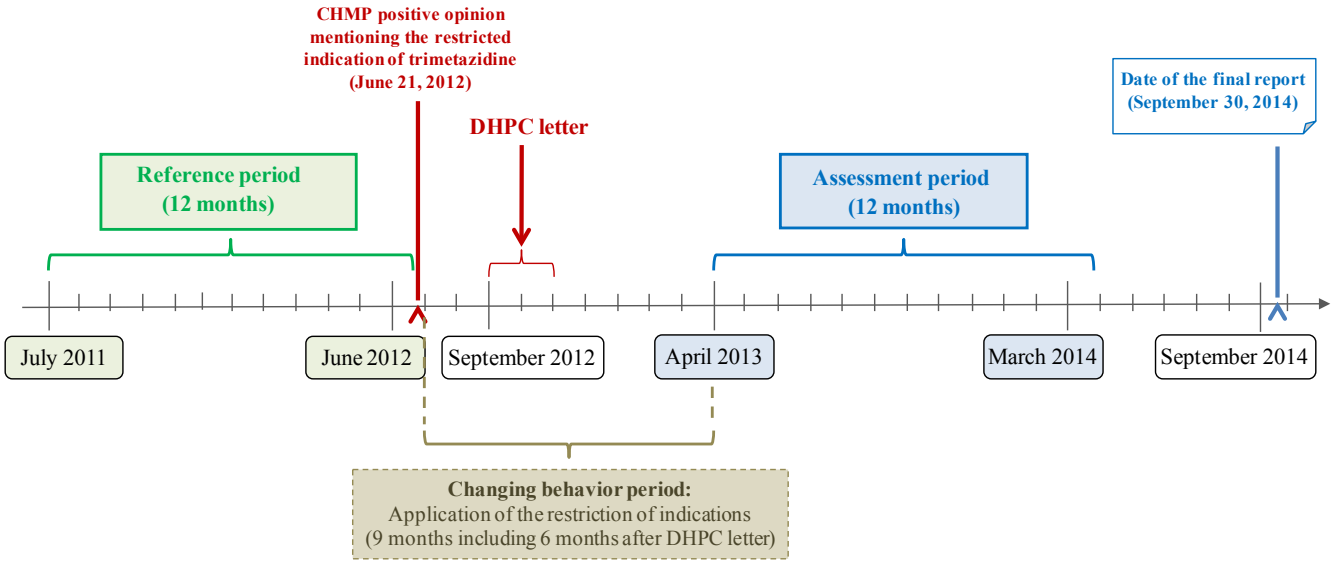
- The two periods must have the same length in order to be comparable.
- The CHMP positive opinion - press release was published on the EMA website mentioning the restricted indication of trimetazidine in cardiology on June 2012 (June 21, 2012). The reference period should be analysed before this date and assessment period after this date.

- The DHPC letter sent to prescribers in the countries where trimetazidine was marketed (from September to October 2012). A transition period of at least six months after sending the DHPC letter seems appropriate before the assessment period in order to allow the physicians to be informed and apply the new restricted indications.
- Overall, according to the number of trimetazidine prescriptions in each country (see Table (10.4.1.2) 2 and Section 10.4.2 for Romania), a collection period of one year is necessary to allow enough prescriptions of trimetazidine. Moreover, the advantage of a full year period for data collection is that it removes any potential bias related to seasonality of prescriptions.
- Constraints linked to the differences of production and publication cycles from one country to another (see Table (10.4.1.2) 1 in Section 10.4 Data sources). Cycles of data collection of are calendar quarters in Spain and France (frequency applicable from 2013 with backdata corrections for the years 2012 and 2011), rolling seasonal semesters in Greece and Poland, and monthly in Romania. Therefore, the bounds of both periods should be synchronous across countries and compatible with these timelines in order not to take a mid-cycle in one of these countries.
- Deadline for the study report submission is 30 September 2014. Therefore, considering one year data collection and given the time lag needed for the data management after its collection in each country (especially in Greece and Poland where data are collected per rolling semesters, see Section 10.4 Data sources), the data collection must start early enough (April 2013) to provide a full year view of complete data.

Thus, the two following extraction periods from the selected databases will be considered Figure (10.2) 1.

- Reference period: one year period before the restriction of trimetazidine in cardiology [*i.e.* before the date of the CHMP positive opinion (June 21, 2012)], from July 2011 to June 2012.
- Assessment period: a one year period beginning six months after sending of the DHPC letter to prescribers in countries where trimetazidine was marketed (*i.e.* after September / October 2012 (2)), from April 2013 to March 2014.

**Figure (10.2) 1 - Main study periods and timelines**




The time between these two extraction periods will not be used for the analysis of the proportion of prescriptions of trimetazidine for ophthalmologic and ENT diagnoses. However, the trends of ophthalmological and ENT prescriptions will be studied during the first months after the announcement of the restriction of indications to allow understanding of the change process.

Of note, even if data are accumulated over a year to produce moving annual trend (MAT), the study is still considered cross-sectional as the pooled extractions are not longitudinal.
Eligible prescriptions for the analysis are those containing trimetazidine, its brand or generic names (see Appendix 1, *i.e.* Annex I of the CHMP opinion where the brand and generic names are listed and limited to the 5 countries where the Drug Utilisation Study will be performed) made by the targeted prescribers (GP, ophthalmologist and ENT specialists).

## 10.3. Variables

The primary end point of interest is the proportion of trimetazidine prescriptions for ophthalmological or ENT diagnoses (within the scope of its past indications) among all trimetazidine prescriptions in the targeted prescribers of each country.

Secondary end points include:

- Extent of prescriptions or deliveries of trimetazidine for the ophthalmological or ENT diagnoses by GPs, ophthalmologists and ENT specialists before and after the restriction of its indications. The distribution of trimetazidine use in its past indications will be expressed across specialties per country.
- Extent of prescriptions or deliveries of trimetazidine for the ophthalmological or ENT diagnoses by specialist' characteristics before and after the restriction of indications.
- Trends of prescriptions or deliveries of trimetazidine for the ophthalmological or ENT diagnoses over time before and after its restriction of indications.

- To study the evolution of physicians' prescribing behaviour over time, the proportions of ophthalmological or ENT diagnoses will be refined by semester.
- The proportion of prescriptions of trimetazidine by GPs in the cardiovascular indication after its restriction of indications (only in IMS PI).
- The proportion of prescriptions of trimetazidine by GPs for angina pectoris without other concomitant prescriptions for angina pectoris, after its restriction of indications. This endpoint can only be defined in the PI databases from France and Spain, where the different lines of prescriptions from a same visit can be linked together.

The two last secondary endpoints will be assessed among GPs since it is assumed unlikely that ophthalmologists or ENTs prescribe trimetazidine in a cardiovascular indication.

The following information will be extracted from each database:
- Prescriber information: specialty (GP, ophthalmologist and ENT specialist), age, gender and region of practice within the country,
- Patient information: age, gender, date and place of the visit (the latter being not available in France and Romania),
- Prescription information: drug name, prescription date, ICD 10 code and label of the diagnosis related to the prescription, information on whether the prescription is an initiation or renewal.
- Ophthalmological and ENT diagnoses, corresponding to the indications of trimetazidine registered before the end of the referral, are defined using the following ICD-10 codes:
  - H 34 : Retinal vascular occlusions,
  - H 35 : Other retinal disorders,
  - H47 : Other disorders of optic [2nd] nerve and visual pathways,
  - H53 to H54: Visual disturbances and blindness,
  - H55: Nystagmus and other irregular eye movements,
  - H81: Disorders of vestibular function,
  - H82: Vertiginous syndromes in diseases classified elsewhere,
  - H83: Other diseases of inner ear,
  - H90: Conductive and sensorineural hearing loss,
  - H91: Other hearing loss,
  - H93: Other disorders of the ear, not elsewhere classified,
  - R42 and its subcodes: Dizziness and giddiness.
- Cardiovascular diagnoses corresponding to the indication of trimetazidine (stable angina pectoris) using the following ICD-10 codes:
  - I20.1: Angina pectoris with documented spasm
  - I20.8: Other forms of angina pectoris
  - I20.9: Angina pectoris, unspecified
  - Medicines with indication for angina pectoris concomitantly prescribed with trimetazidine:
    - B01A: Antithrombotic agents
    - C01D: Vasodilatators used in cardiac diseases
    - C01EB17: Ivabradine
    - C01EB18: Ranolazine
    - C07: Beta-blocking agents
    - C08: Calcium channel blockers
    - C09: Agents acting on the renin-angiotensin system

In each country, the endpoints will be assessed among three subgroups based on the specialty of the prescriber, when applicable:

- General practitioners (in some countries this includes family physicians and residents in internal medicine), definition of GP is provided in (Appendix 2),
- Ophthalmologists,
- ENT specialists.

## 10.4. Data sources

Databases containing prescriptions made by the prescribers (GPs, Ophthalmologists and ENTs specialists) or the delivery of these prescriptions in pharmacy will be used:

- Prescribing insights (PI) is a common name for a set of country specific databases containing drug prescriptions, their corresponding diagnoses as well as the specialty of prescribers. PI is available in France, Greece, Poland and Spain.
- National Diagnostic Index™ (NDI):
  National diagnostic index (NDI) contains drug deliveries in pharmacy, their corresponding diagnoses and the specialty of the prescriber. NDI is available in Romania.

For both databases, a validation process for ICD-codes is set-up as described in the following sections.

### 10.4.1. Prescribing Insights (PI) database

#### 10.4.1.1. General description of PI database

PI database contains the evolution of IMS Medical Indices, which had as objective to provide a detailed analysis of prescriptions, diagnoses and therapy patterns based on the records of practicing physicians (both GPs and specialists). These have been used in many countries since 1959. The reports are being published in over 40 countries. They are issued since 1963 in France, 1969 in Spain, 1986 in Greece and 1995 in Poland (Appendix 3).

The data contained in PI panel is contributed by a panel of physicians randomly selected in each country. The number of physicians participating in the panel varies from country to country and from specialty to specialty. An annual renewal of 20-30% is performed on the panel, *i.e.* either decided in advance or forced (for example 25% in France and 30% in Spain) or the natural churn. A forced panel renewal means that physicians have a maximum number of years for participation in the panel (*e.g.* maximum four years for France). Each of these induced or natural turn over strategies has its own advantages (Appendix 4).

#### 10.4.1.2. Sampling design of PI database

Physicians are stratified mainly according to their specialty and region (Table (10.4.1.2) 1; Appendix 4).

Note that in Spain, the physicians are stratified by centre size, region (proportional) and specialty (disproportional). In France, the sampling is performed using more criteria, especially for GPs (activity score, age, sex, demographic size of their practice's place).

**Table (10.4.1.2) 1 - Countries Characteristics of PI panel - EEA Countries**

| Characteristics | FRANCE | GREECE | POLAND | SPAIN |
|---|---|---|---|---|
| 1st Year of issue | 1963 | 1986 | 1995 | 1969 |
| Physician Panel Size | 1 190 Doctors | 474 doctors | 565 Doctors | 965 Doctors |
| Panel selection method, sampling | Random sample | Random cluster sample | Random sample | Random sample |
| Stratification | Stratified by region and speciality | Stratified by Region and Specialty | Stratified by speciality | Stratified by region, centre size (proportional) and speciality (disproportional) |
| Reporting Time | 7 Consecutive Days | 7 Consecutive Days | 7 Consecutive Days per semester | 7 Consecutive Days |
| Publication cycle | Up to 2012: seasonal Quarters - Spring (Mar - May), Summer (Jun - Aug), Autumn (Sep - Nov), Winter (Dec - Feb). From 2013: Calendar Quarters* | Rolling Semesters with quarterly delivery | Rolling Semesters : Q1 and Q3 (October-March, April-September) , Q2 and Q4 (January-June, July-December) | Calendar Quarters |
| Geographic | All 8 regions, except for overseas islands | All 7 regions | All 3 regions | All regions except Las Palmas, Tenerife, Ceuta and Melilla |

** Back data: For the calendar quarter transition in 2013, the years 2012 and 2011 will be recalculated in calendar quarter.*

The number of GPs, ENTs and ophthalmologists in PI panel for countries of interest is shown in Table (10.4.1.2) 2. Note that in Greece the panel does not cover ophthalmologists.

**Table (10.4.1.2) 2 - Focus on trimetazidine - Number of specialists participating in the PI panel and number of trimetazidine prescriptions - EEA Countries**

| Number (%) | FRANCE | GREECE** | POLAND* | SPAIN* |
|---|---|---|---|---|
| GPs Universe | 60 974 | - | 14218 | 49 121 |
| GPs in the PI panel | 400 (0.66) | (1.63) | 110 (0.77) | 300 (0.61) |
| ENTs Universe | 2 228 | - | 2564 | 2598 |
| ENTs in the PI panel | 40 (1.79) | (1.74) | 25 (0.98) | 30 (1.16) |
| Ophthalmologists Universe | 4 716 | Not covered | NA | NA |
| Ophthalmologists in the PI panel | 60 (1.27) | (0) | NA | NA |
| Number of trimetazidine prescriptions (last MAT) except cardiologists | ± 1 450 | ± 650 | ± 1450 | ± 390 |

*(*) In Spain, the GPs and family doctors are accumulated. In Poland, family doctors and the resident physicians are considered as GPs.*
*(**) For Greece the panel size is expressed in % of physicians compared to the corresponding universe.*
*MAT: Moving annual Trend;*
*NA: Not applicable: the ophthalmological indication has never been registered in these countries.*

#### 10.4.1.3. Data collection of PI database

Physicians are asked to collect data during 7 consecutive days, including the week-end, for each publication cycle (*i.e.* each quarter for France and Spain, or semester for Greece and Poland). During this period, they use a paper notebook or an electronic padbook (Appendix 5 and Appendix 6) to record all their prescriptions for each patient visited in outpatient care.

Since first quarter of 2013, all participating physicians in Spain have the possibility to use padbooks or to keep participating in the panel *via* paper notebooks. Greece and Poland will also offer to the physicians the possibility of using padbooks by the end of 2014. Data collection through padbooks is planned in France in the upcoming years, but will not happen in 2014.

The following information is available for each prescriber: Age, gender, specialty, region of practice, and in some cases, the type of practice (office-based, office and hospital based).

The following information is available for each prescription:

- Date of patient's visit, patient's age, gender, place of visit (ambulatory, doctor's, patient's home, surgery, external clinic or other),
- Diagnosis (one or several), or the main symptoms (diagnoses are coded according to the ICD-10 classification),
- Drug prescription: list of the drugs prescribed (coded in ATC), desired effects expected from administering each drug, avoiding such generalities as "healing", "improvement" etc.

#### 10.4.1.4. Coding reliability and quality control during data release of PI database

For each country, the data collected *via* paper notebooks or padbooks are transmitted to a dedicated team called IMS central coding unit.

For the paper notebooks, diagnoses verbatim reported by the physicians are coded to ICD-10 codes by this team using a mapping algorithm developed and enhanced by IMS since 1990s. This coding is carried out using the same coding guidelines translated into different languages to ensure harmonization. Coders are fully fluent on the local languages of the countries they code. They are supervised by Healthcare Professionals (HCP) including medical doctors and nurses who provide medical and scientific supporting during coding steps and check randomly 5% of coded prescriptions from each coder to ensure the quality level. HCPs are trained on IMS tools and have to follow IMS SOPs within the framework of their activities. Moreover, the quality unit of the production department of IMS verifies continuously the quality of its panels in terms of panel representativeness, consistency of collected data and validation of coding of physician' verbatim.
Drugs, diagnoses and patient's characteristics from PI databases are recorded and coded separately into three different data entry forms.

Before the release of the data collected at each quarter/semester, inconsistencies (*i.e.,* between diagnoses/drugs and patients' characteristics (age, gender): reporting of pregnancy for a male patient or prostate cancer for a female patient, …) are automatically detected (programmed rules) and then adjudicated by an IMS Health Care Professionals (the inconsistency is checked *versus* the original paper notebooks and is either corrected or tagged as aberrant data in the database).

A customized report is sent to all participating prescribers at each end participating quarter or semester in order to provide them an overview of their own activity and of the quality of the data they have forwarded to IMS Health.

For the padbooks, the physician can choose between selecting a diagnosis from a drop down list which is already linked to an ICD-10 code or entering free text that is then coded by IMS (same coding system as paper notebooks mentioned above).

The coding process in the PI database is homogenous between countries and over time and continuously validated through an internal IMS process made at each quarter or semester release.

### 10.4.2. National Diagnostic Index (NDI) database

#### 10.4.2.1. General description of NDI database

In Romania, the National Diagnostic Index (NDI) database is a national claims database containing information collected through 4000 pharmacies out of the 7700 registered (last update dated April 2014), allowing to cover around 90% of the drug dispensing across the country. Data are collected from all patients covered by state health insurance are used by the National Health Insurance Fund (NHIF).

#### 10.4.2.2. Coding process and reliability of NDI database

When a physician prescribes a medicinal product to a patient, the physician specifies on the prescription form the following information:

- the patient's characteristics (name, age and gender),
- the drug (molecule, brand name, dose),
- the diagnosis associated with the prescription according to a national list consisting of 999 disease codes.

At the pharmacy level, for each prescription, the name/specialty of the physician, the date of delivery, units dispensed and all the above information documented by the physician are manually entered into the reporting software by the pharmacist.

The diagnoses from this local coding list are then matched to ICD-10 codes through a validated and continuously updated thesaurus system in a centralised electronic platform (IMS Health has no control over this coding as this is carried out by the governmental bodies in charge of this database). Once the pharmacist has entered the data into the software, there is no intervention from the pharmacist nor specific validation for coding, even if codes are missing or incorrect.
Of note, complementary information on the delivered products are also automatically generated by the software through a reference product file: ATC code, reimbursement status, product manufacturer, type of pack …

Various topics are available for analysis (e.g. product manufacturer, therapeutic class of drug, molecule, administration form, launching year, diagnosis, etc.). A complete set of measures are also available (e.g. units, value on three price levels, counting units, etc).

Excerpts of this database are accessible to IMS through monthly reports of aggregated data, including all possible combinations of prescribed drug, concomitant treatments, and diagnoses related to each prescription, specialty of the prescriber, patient gender and age group (see Appendix 7). If the ICD-10 codes have not been entered into the software, they are considered as *"missing"* for the analysis.

### 10.5. Study size

The calculation of the sample size is based on the primary objective, *i.e.* the proportion of prescriptions of trimetazidine for ophthalmological and ENT diagnoses (within the scope of its past indications) among all prescriptions of this drug in each country. The following formula was used for the calculation of the sample size, in which n is the required sample size, t is the t-test value for a given confidence interval, p is the proportion of trimetazidine prescriptions for ophthalmological or ENT diagnoses, and e is the error margin.

$$n = t^2 . \frac{p.(1-p)}{e^2}$$

Since there is no evidence supporting the expected proportion of trimetazidine prescription for ophthalmological or ENT diagnoses after the restriction of trimetazidine indications, to be on the safe side, it has been considered a p as 50% (this assumption yields the largest sample size). Given this assumption, and for a confidence interval of 95% (t=1.96) and an error margin (e) of 5%, the required **sample size would be 384 prescriptions for each country.**

According to the last available Moving Annual Trend (MAT), the number of prescriptions of trimetazidine observed over one year in France, Greece, Poland and Spain is higher than the threshold of N=384 prescriptions (see Table (10.4.1.2) 2 above). Therefore, data collected over one year for the Reference period will be enough for statistical analyses. Concerning the assessment period, it is difficult to produce reliable predictions of the level of prescriptions at the time this protocol is being written, but data collection over one year should be sufficient for statistical analysis in most of the 4 countries if the overall number of prescriptions of trimetazidine remain in the same range and does not drop dramatically following its restriction of indications (see Section 10.9).

The need for an extension of data collection for the assessment period will be assessed in August 2014 (once the data from the last quarter ending by March 2014 will be made available). Indeed, depending on the observed number of prescriptions and the level of the estimated proportion of prescriptions for ophthalmological and ENT diagnoses among all prescriptions, the required sample size may be revised while keeping the needed statistical precision.

In Romania, due to the nature (national claims database) and coverage rate (88%) of NDI, the threshold of 384 deliveries will be exceeded for both periods.

## 10.6. Data management

The study will be conducted according to the standard operating procedures of IMS Health. The datasets extracted from each country database are stored in a dedicated database and checked in terms of consistency before the data analysis. Once validated and quality checked, the database will be locked.

## 10.7. Data analysis

### 10.7.1. General statistical considerations

The statistical analysis will be conducted using SAS® software Version 9.2 for Windows ™ (SAS Institute, North Carolina, USA).
Continuous variables will be described by their number (number of valid cases, number of missing values), mean, standard deviation, median, Q1, Q3, minimum, and maximum.
Categorical variables will be described as the total number and relative percentage per category.

The number of missing data will be indicated. Missing values are expected to be non-substantial and distributed at random. As no applicable methods of addressing missing values win unanimous support, no missing data will be replaced (3). Especially, prescriptions of trimetazidine reported without the indication or diagnosis will not be taken into account for the calculation of the percentages. The reasons for non-response will be sought, especially from all observed variables. This will ensure that missing data are reported with enough detail to strengthen the validity of the results, as recommended by the STROBE guidelines (4).
Confidence intervals of 95% will be calculated for each item, when relevant.
The statistical unit will be the prescription (for extractions from PI database) or the dispensed prescription (for extractions from NDI database). Calculations will be performed on raw data. Thus, no projection factor will be applied to generalize the results to the entire prescribers' universe.

Summaries will be reported at country level and by period (Reference period and Assessment period) stratified according to the speciality (GPs, ophthalmologists and ENTs).
Results (see secondary end point *ii* in Section 10.7.3 Descriptive analysis) will be analyzed also according to prescribers' characteristics to check for possible selection bias.

### 10.7.2. Assessment of selection bias in PI panel

Prescribers' profile will be described per country: age, gender and regions.
Note that the data extractions will contain only GPs, ophthalmologists and ENT specialists with at least one prescription of trimetazidine over each period. As a result, prescribers' profile could deviate from that of the universe just because prescribers are different and not due to a potential bias in the databases used.

In PI database, to assess the potential of any selection bias due to the participation in the panel, characteristics of long time panellists will be compared to more recent ones according to their age, gender and regions. This is subject to availability of information and sufficient number of prescribers in each PI database.

As the panel turn-over is around 25%, the new panellists are defined as those 25% of panellists who have the shortest duration of participation in the panel. Others would be considered as long time panellists.

As the NDI database coverage is national, the analysis of selection bias will not be carried out (also technically, it is not possible to reach prescribers).

**Table (10.7.2) 1 - Characteristics of trimetazidine prescribers by specialty and per country**

| | **France** | | | **Greece** | | | **Poland** | | | **Spain** | | | **Romania** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **By specialty** | Overall | Long time | Recent | Overall | Long time | Recent | Overall | Long time | Recent | Overall | Long time | Recent | Over all | Long time | Recent |
| **GPs** | | | | | | | | | | | | | | | |
| Demographics | | | | | | | | | | | | | | | |
| Age | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx |
| Gender | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx |
| Regions/ Geographic area | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx |
| **ENTs** | | | | | | | | | | | | | | | |
| Demographics | | | | | | | | | | | | | | | |
| Age | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx |
| Gender | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx |
| Regions/ Geographic area | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx |
| **Ophthalmologists** | | | | Not covered | Not covered | Not covered | NA | NA | NA | NA | NA | NA | | | |
| Demographics | | | | | | | | | | | | | | | |
| Age | xxx | xxx | xxx | | | | | | | | | | xxx | xxx | xxx |
| Gender | xxx | xxx | xxx | | | | | | | | | | xxx | xxx | xxx |
| Regions/ Geographic area | xxxx | xxxx | xxxx | | | | | | | | | | xxxx | xxxx | xxxx |

*NA: Not applicable: the ophthalmological indication has never been registered in these countries. Not covered: The PI database in this country does not cover ophthalmologists.*

## 10.7.3. Descriptive analysis

Primary end point

The use of trimetazidine in its past ophthalmological and ENT indications will be analysed using the prescriptions/deliveries collected during the assessment period.
Nine months after the restriction of its indication in cardiology, all prescriptions/deliveries of trimetazidine will be extracted over one year, *i.e.* from April 2013 to March 2014 (two consecutive semesters in case of PI database and 12 months in case of NDI database).
Two groups of trimetazidine prescriptions/deliveries will be identified according to the filled diagnosis: (a) ophthalmological diagnoses and (b) ENT diagnoses (as defined in Section 10.3) among (c) the total of diagnoses. This total will include all other diagnoses. In case there are any missing values for diagnosis, they will be separated in the table, but will not be included in the total of diagnoses.

Ophthalmological and ENT use will be calculated as: (a+b)/c. Percentages of use during the assessment period will be expressed per country for GP's, ophthalmologists and ENT specialists altogether (Table (10.7.3) 1).

**Table (10.7.3) 1 - Prescriptions/deliveries of trimetazidine during the assessment period by diagnosis and per country**

| Assessment period | France | Greece | Poland | Spain | Romania |
|---|---|---|---|---|---|
| **Count of prescriptions or deliveries:** | | | | | |
| Ophthalmological diagnoses (a) | xxx | xxx | xxx | xxx | xxx |
| ENT diagnoses (b) | xxx | xxx | xxx | xxx | xxx |
| Missing diagnoses | xxx | xxx | xxx | xxx | xxx |
| Total of diagnoses† (c) | xxx | xxx | xxx | xxx | xxx |
| **Use in past indications (%)** (a+b)/c | xx.x% | xx.x% | xx.x% | xx.x% | xx.x% |
| **CI 95%** | [xx.x%-xx.x%] | [xx.x%-xx.x%] | [xx.x%-xx.x%] | [xx.x%-xx.x%] | [xx.x%-xx.x%] |

*† Total not including missing diagnoses.*

A sensitivity analysis based on the interrupted time series (ITS) design could be added if the extension of the data collection for the "assessment period" is deemed necessary (please refer to section 10.5) and if the final number of observation points (i.e. quarters) before and after the intervention are large enough to provide meaningful trends for an ITS.

Secondary end points

i. *Extent of prescriptions/deliveries of trimetazidine for the ophthalmological or ENT diagnoses by GPs, ophthalmologists and ENT specialists before and after the restriction of its indications.*
   For each country, the distribution of the prescriptions or deliveries across the specialties will be given in Table (10.7.3) 2.

**Table (10.7.3) 2 - Distribution of ophthalmological and ENT prescriptions or deliveries of trimetazidine during the assessment period by specialty and per country**

| Assessment period | France | Greece | Poland | Spain | Romania |
|---|---|---|---|---|---|
| **Count and % of use in past ophthalmological and ENT indications of trimetazidine prescriptions or deliveries:** | | | | | |
| by GPs | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |
| by ENTs | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |
| by ophthalmologists | xx (xx.x%) | Not covered | NA | NA | xx (xx.x%) |
| **All s** | xx (100%) | xx (100%) | xx (100%) | xx (100%) | xx (100%) |

*NA: Not applicable: the ophthalmological indication has never been registered in these countries. Not covered: The PI database in this country does not cover ophthalmologists.*

Moreover, proportions will be calculated per country and specialty for the two time periods (Table (10.7.3) 3).

Although trimetazidine does not have ophthalmological indication in Poland and Spain, all diagnoses, including ophthalmological indications, will be analysed in these two countries for the GPs in order to avoid bias and keep the coherence with the analysis performed for the other countries.

**Table (10.7.3) 3 - Proportion of trimetazidine prescriptions/deliveries for ophthalmological or ENT diagnoses per country, before and after the restriction of indications by specialty (continued)**

| | France | | Greece | | Poland | | Spain | | Romania | |
|---|---|---|---|---|---|---|---|---|---|---|
| **By specialty** | **Reference period** | **Assessment period** | **Reference period** | **Assessment period** | **Reference period** | **Assessment period** | **Reference period** | **Assessment period** | **Reference period** | **Assessment period** |
| **GPs** | | | | | | | | | | |
| **Count of prescriptions/deliveries:** | | | | | | | | | | |
| Ophthalmological diagnoses | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx |
| ENT diagnoses | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx |
| Missing diagnoses | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx |
| Total of diagnoses † | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx |
| **Proportion of use in past ophthalmological or ENT indications** | xx.x% (1) | xx.x% (2) | xx.x% (1) | xx.x% (2) | xx.x% (1) | xx.x% (2) | xx.x% (1) | xx.x% (2) | xx.x% (1) | xx.x% (2) |
| **CI 95%** | [xx.x%-xx.x%] | [xx.x%-xx.x%] | [xx.x%-xx.x%] | [xx.x%-xx.x%] | [xx.x%-xx.x%] | [xx.x%-xx.x%] | [xx.x%-xx.x%] | [xx.x%-xx.x%] | [xx.x%-xx.x%] | [xx.x%-xx.x%] |
| **Differentials:** | | | | | | | | | | |
| absolute (Assessment (2)-Reference (1)) | | -xx | | -xx | | -xx | | -xx | | -xx |
| relative (Assessment (2)-Reference (1))/Reference (1) | | -x.x% | | -x.x% | | -x.x% | | -x.x% | | -x.x% |
| CI **95%** for the absolute difference | | [x.x%-x.x%] | | [x.x%-x.x%] | | [x.x%-x.x%] | | [x.x%-x.x%] | | [x.x%-x.x%] |
| **ENTs** | | | | | | | | | | |
| **Count of prescriptions/deliveries:** | | | | | | | | | | |
| Ophthalmological diagnoses | xxx | xxx | xxx | xxx | NA | NA | NA | NA | xxx | xxx |
| ENT diagnoses | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx |
| Missing diagnoses | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx |
| Total of diagnoses† | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx |
| **Proportion of use in past ophthalmological or ENT indications** | xx.x% (1) | xx.x% (2) | xx.x% (1) | xx.x% (2) | xx.x% (1) | xx.x% (2) | xx.x% (1) | xx.x% (2) | xx.x% (1) | xx.x% (2) |
| **CI 95%** | [xx.x%-xx.x%] | [xx.x%-xx.x%] | [xx.x%-xx.x%] | [xx.x%-xx.x%] | [xx.x%-xx.x%] | [xx.x%-xx.x%] | [xx.x%-xx.x%] | [xx.x%-xx.x%] | [xx.x%-xx.x%] | [xx.x%-xx.x%] |
| **Differentials:** | | | | | | | | | | |
| absolute (Assessment (2)-Reference (1)) | | -xx | | -xx | | -xx | | -xx | | -xx |
| relative (Assessment (2)-Reference (1))/Reference (1) | | -x.x% | | -x.x% | | -x.x% | | -x.x% | | -x.x% |
| CI **95%** for the absolute difference | | [x.x%-x.x%] | | [x.x%-x.x%] | | [x.x%-x.x%] | | [x.x%-x.x%] | | [x.x%-x.x%] |

**Table (10.7.3) 3 - Proportion of trimetazidine prescriptions/deliveries for ophthalmological or ENT diagnoses per country, before and after the restriction of indications by specialty 5**

| | France | | Greece | | Poland | | Spain | | Romania | |
|---|---|---|---|---|---|---|---|---|---|---|
| **By specialty** | **Reference period** | **Assessment period** | **Reference period** | **Assessment period** | **Reference period** | **Assessment period** | **Reference period** | **Assessment period** | **Reference period** | **Assessment period** |
| **Ophthalmologists** | | | Not Covered | Not Covered | NA | NA | NA | NA | | |
| **Count of prescriptions/deliveries:** | | | | | | | | | | |
| Ophtalmological diagnoses | xxx | xxx | | | | | | | xxx | xxx |
| ENT diagnoses | xxx | xxx | | | | | | | xxx | xxx |
| Missing diagnoses | xxx | xxx | | | | | | | xxx | xxx |
| Total of diagnoses † | xxxx | xxxx | | | | | | | xxxx | xxxx |
| **Proportion of use in past ophthalmological or ENT indications** | xx.x% (1) | xx.x% (2) | | | | | | | xx.x% (1) | xx.x% (2) |
| **CI 95%** | [xx.x%-xx.x%] | [xx.x%-xx.x%] | | | | | | | [xx.x%-xx.x%] | [xx.x%-xx.x%] |
| **Differentials:** | | | | | | | | | | |
| absolute (Assessment (2)-Reference (1)) | | -xx | | | | | | | | -xx |
| relative (Assessment (2)-Reference (1))/Reference (1) | | -x.x% | | | | | | | | -x.x% |
| CI 95% for the absolute difference | | [x.x%-x.x%] | | | | | | | | [x.x%-x.x%] |

*† Total of diagnoses not including missing diagnoses.*
*NA: Not applicable: the ophthalmological indication has never been registered in these countries.*
*Not covered: The PI database in this country does not cover ophthalmologists.*

*ii. Extent of prescription of trimetazidine for the ophthalmological or ENT diagnoses with regards to GPs, ophthalmologists and ENTs specialists' characteristics before and after the restriction of its indications.*

Physicians will be compared depending on their length of participation in the panel (only for PI databases, *i.e.* all countries except Romania): long time panellists *versus* recent one (Table (10.7.3) 4). The threshold could be fixed with the aid of the 25th percentile: long-time members if duration is longer, new members otherwise.

**Table (10.7.3) 4 - Part of use of trimetazidine in its past ophthalmological and ENT indications per country before and after the restriction of indications by prescribers' characteristics (length of participation in the panel)**

| | France | | Greece | | Poland | | Spain | |
|---|---|---|---|---|---|---|---|---|
| **By type of participating physicians** | **Reference period** | **Assessment period** | **Reference period** | **Assessment period** | **Reference period** | **Assessment period** | **Reference period** | **Assessment period** |
| **Long-time members** | n | n | n | n | n | n | n | n |
| **Count of prescriptions:** | | | | | | | | |
| Use of trimetazidine in its past ophthalmological or ENT indications | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx |
| Total of diagnoses | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx |
| **Proportion of use in past ophthalmological or ENT indications** | xx.x% | xx.x% | xx.x% | xx.x% | xx.x% | xx.x% | xx.x% | xx.x% |
| **Differentials:** | | | | | | | | |
| absolute (Assessment (2)-Reference(1)) | | -xx | | -xx | | -xx | | -xx |
| relative (Assessment (2) – Reference (1)) / Reference (1) = (3) | | -x.x% | | -x.x% | | -x.x% | | -x.x% |
| **Recent or new members** | n | n | n | n | n | n | n | n |
| **Count of prescriptions:** | | | | | | | | |
| Use in past indications | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx |
| Total of diagnoses | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx | xxxx |
| **Proportion of use in past ophthalmological or ENT indications** | xx.x% | xx.x% | xx.x% | xx.x% | xx.x% | xx.x% | xx.x% | xx.x% |
| **Differentials:** | | | | | | | | |
| absolute Assessment (2)-Reference(1)) | | -xx | | -xx | | -xx | | -xx |
| relative (Assessment (2) – Reference (1)) / Reference (1) = (4) | | -x.x% | | -x.x% | | -x.x% | | -x.x% |
| **Long time vs recent or new members** | | | | | | | | |
| **Delta** in points (3)-(4) | | x.x | | x.x | | x.x | | x.x |

*iii. Trends of prescriptions/deliveries of trimetazidine for the ophthalmological or ENT diagnoses over time before and after its restriction of indications.*

To study the evolution of physicians' prescription behaviour over time, the proportions of ophthalmological or ENT diagnoses will be refined by semester: two semesters before the restriction of indications (Reference period from July 2011 to June 2012) and two semesters after (Assessment period from April 2013 to March 2014).

Box plots or bar charts with confidence intervals will be used to illustrate the trends.

Analysis results of all the selected countries will be presented in the same statistical report, and then in the same study report.

*iv. Extent of prescriptions/deliveries of trimetazidine in the cardiovascular indication in the GP sub-panel after the restriction of its indications.*

For each country except Romania, the count of the prescriptions in the cardiovascular indication will be given in Table (10.7.3) 5 for the assessment period. In NDI database (Romania), this end point is not assessable, as only aggregated data are provided to IMS. Note that this analysis will be performed at the prescription level, and not at the patient level.

In case a prescriber uses "renewal" as the reason of prescription without mentioning the cardiovascular diagnosis/indication, this may result in an underestimation of the proportion of patients receiving trimetazidine in the cardiovascular indication. For prescriptions with available data on their status (initiation versus renewal), separate analyses will be performed for prevalent users (renewals) and incident users (initiations) to check whether the proportion of trimetazidine prescriptions with a cardiovascular indication differ between groups.

**Table (10.7.3) 5 - Proportion of cardiovascular prescriptions of trimetazidine among GPs and per country after the restriction of its indications**

| | **France** | **Greece** | **Poland** | **Spain** |
|---|---|---|---|---|
| | **Assessment period** | | | |
| **Among GPs** | n | n | n | n |
| **Count of all TMZ prescriptions:** | | | | |
| Use of trimetazidine in cardiovascular indication | xxx | xxx | xxx | xxx |
| Total of diagnoses † | xxxx | xxxx | xxxx | xxxx |
| **Proportion of use in cardiovascular indication** | xx.x% | xx.x% | xx.x% | xx.x% |
| **Count of TMZ renewals:** | | | | |
| Use of trimetazidine in cardiovascular indication | xxx | xxx | xxx | xxx |
| Total of diagnoses † | xxxx | xxxx | xxxx | xxxx |
| **Proportion of use in cardiovascular indication** | xx.x% | xx.x% | xx.x% | xx.x% |
| **Count of TMZ initiations:** | | | | |
| Use of trimetazidine in cardiovascular indication | xxx | xxx | xxx | xxx |
| Total of diagnoses † | xxxx | xxxx | xxxx | xxxx |
| **Proportion of use in cardiovascular indication** | xx.x% | xx.x% | xx.x% | xx.x% |

*† Total of diagnoses not including missing diagnoses.*

*v. Extent of prescriptions/deliveries of trimetazidine for angina pectoris in the GP sub-panel without other concomitant prescriptions for angina pectoris after the restriction of its indications.*

For France and Spain, the count of the prescriptions of trimetazidine carried out by GPs for angina pectoris without other concomitant prescriptions for angina pectoris will be given in Table (10.7.3) 6 for the assessment period.

**Table (10.7.3) 6 - Proportion of prescriptions of trimetazidine for angina pectoris without linked prescriptions for angina pectoris, during the assessment period - France and Spain - among GPs**

| Assessment period | France | Spain |
|---|---|---|
| Among GPs | n | n |
| Count of trimetazidine prescriptions for angina pectoris | xx | xx |
| **Count and % of trimetazidine prescriptions for angina pectoris without linked concomitant prescriptions for angina pectoris** | xx (xx%) | xx (xx%) |

## 10.8. Quality control

The quality control is conducted at two or three levels depending on the database (PI /NDI):

- At the panel management level in case of PI databases, any efforts is undertaken to collect complete and valid data (support for physicians, quality control, induction of panel turn over…).
- At the database level, the quality unit of the production department of IMS verifies continuously the quality of its numerous panels in terms of panel representativeness, consistency of collected data, and validation of coding of physicians' verbatim. The documents can be consulted on site.
- At the study level, all aspects of the study from protocol development to the reporting of the results are conducted following standard operating procedures (SOPs) of IMS HEOR department. Specifically, the classification of diagnoses collected for trimetazidine under ophthalmological or ENT areas will be validated by a physician. SOPs of IMS HEOR can be consulted on site.

For details on the panel and coding procedures see Section 10.4.

## 10.9. Limitations of the research methods

### Definition of cardiovascular indication

The PI and NDI databases are prescription-based (the statistical unit is the prescription) and cross-sectional (patient's history is not available), thus the complete ascertainment of the patient's cardiovascular history is not possible in the current study.

In the PI databases (France, Greece, Poland and Spain), the physicians record information during 7 consecutive days per publication cycle (corresponding to a quarter in France and Spain, and to a semester in Greece and Poland). Therefore, given that both the reference and the assessment periods cover several publication cycles, a patient receiving trimetazidine renewal prescriptions may count several times without possibility to link these different visits to a single patient. For this reason, analyses can be performed at the prescription level, but not at the patient level.

As trimetazidine is a chronic treatment, a prescriber may proceed to its renewal without explicitly mentioning the cardiovascular diagnosis/indication. This type of information bias due to misclassification would lead to underestimate the true proportion of patients receiving trimetazidine in the cardiovascular indication. However, for prescriptions with the renewal/initiation mentioned as type (and not as diagnosis) by the prescriber, a separate analysis can be performed to see if the proportion of trimetazidine prescriptions with a cardiovascular indication differs between these two groups.

Note also that in NDI database (Romania), only aggregated data are provided to IMS. As a consequence, such analysis is not possible.

**Definition of ophthalmological and ENT diagnoses**
This study focuses on ophthalmological and ENT diagnoses of trimetazidine within the scope of its past indications. As a result, ophthalmological or ENT diagnoses associated with trimetazidine which are not part of its past indications will be counted with all other prescriptions. The present study does not aim to assess all cases of off label use. As a result, the provided definition of ophthalmological and ENT diagnoses using ICD 10 codes are in line with study objectives.

**Definition of concomitant medication for angina pectoris**
Only drugs co-prescribed to a patient at the same visit are collected in the PI databases. However, a patient with a trimetazidine prescription may have some concomitant medication for angina pectoris that was prescribed at a different visit than the one registered in the PI databases, thus underestimating the proportion of trimetazidine prescriptions for angina pectoris without concomitant medication for angina pectoris.

**Panel composition and representativeness**
In Greece, PI panel does not include ophthalmologists. Analyses will thus be limited to the diagnoses reported by GPs and the ENTs specialists.
In Poland and Greece, data integration in PI databases is performed every quarter alternatively for half of the panel, and the complete update of the information is obtained after two quarters. This implies to take a year of prescriptions from date to date and to make sure that a whole semester is covered.

It may be argued that the physicians who participate in panels may have different practice behaviour than other physicians who do not take part in such activity. In PI database, panel members are recruited through stratified random sampling from a universal list of practitioners. In France, Greece, Poland and Spain (PI databases), physician's specialty and characteristics such as age, gender and region are taken into account at the moment of the recruitment for the panel to ensure that it is representative of the population of prescribers. The number of specialists needed in the sample is determined at the time of the panel design and mainly proportional to the number of specialists in the country. However, to make sure of the applicability of statistical tests for specialists whose absolute number in the population is low, disproportionally larger numbers are often considered to compensate their rarity as compared to general practitioners. In case of analysis of extrapolated numbers, the results are then weighted to take into account any disproportionality in the sample. By design, the panel and its composition, including the number of specialists, provide a representative picture of the off-label use of trimetazidine in each country as a whole. Moreover, the data generated from these databases are checked against external sources of data to ensure their representativeness.

Moreover, a turnover of 20-30% according to the country (e.g. 25% per year in France and 30% in Spain) in each panel shows a good renewal of doctors. However, to make sure that use of trimetazidine in its past indications is not associated with characteristics of doctors within the panel (*i.e.* those who are long time panellist do not have necessarily different practice behaviour), the proportion of use of trimetazidine in its past indications among different groups of physicians with longer or shorter panel history will be analysed.

In Romania, the NDI database allows covering a wider population of prescribers compared to PI database (more than 90% of the drug deliveries). As a consequence, the coverage of specialists in the panel is nationally representative.
The prescriptions are recorded only if the drug is dispensed.

**Study feasibility**
The number of trimetazidine prescriptions (from GPs, ophthalmologists and ENTs) reported in the last available Moving Annual Trend (MAT1) should provide a sufficient sample size. However, it is likely that the number of prescriptions in the ophthalmological and ENT indications decrease after the CHMP positive opinion (June 21, 2012) - press release, published on the EMA website mentioning the restricted indication of trimetazidine in cardiology and the DHPC letter sent to the prescribers in the countries where trimetazidine is marketed. In this case, the expected confidence interval may not be achieved or it may become necessary to extend the data collection period.

**Missing diagnoses**
On the basis of the feasibility study, it appears that prescriptions or deliveries of trimetazidine reported without the diagnosis are rare. They are coded through ICD-10 code 'R693 Not stated diagnosis documentation' and represent less than 1% of cases. No systematic reason for non-response appears (not always the same prescriber, various patient profiles, at different times of the year). As a result, the planned method to handle missing data in the analysis seems to be suitable.

## 11. PROTECTION OF HUMAN SUBJECTS

This study is non-interventional and based on secondary data use. No identifying data is collected in any of selected databases. These databases are set up following local law, including data privacy regulation.

## 12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable, as the study will be carried out through secondary use of data already collected.

## 13. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study report should be sent to the MSs on September 30, 2014.

1 From Quarter 2-2011 to Quarter 1-2012 for France, from Quarter 3-2011 to Quarter 2-2012 for Greece, Poland, Spain and Romania.

## 14. REFERENCES

1. European Medicines Agency - Human medicines - European Medicines Agency recommends restricting use of trimetazidine-containing medicines [Internet]. [cited 2012 Oct 15]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/public_health_alerts/2012/06/human_pha_detail_000063.jsp&mid=WC0b01ac058001d126
2. European Medicines Agency - - European Medicines Agency recommends restricting use of trimetazidine-containing medicines [Internet]. [cited 2012 Oct 15]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/public_health_alerts/2012/06/human_pha_detail_000063.jsp&mid=
3. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.
4. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008 Apr;61(4):344–9.

# 15. APPENDICES

## Appendix 1: List of the names, pharmaceutical form(s), strength(s) of the medicinal product(s), route(s) of administration, marketing authorisation holder(s) in the member states presented for France, Greece, Poland, Romania and Spain

| Country | Address | Name | Dosage | Form | Route |
|---|---|---|---|---|---|
| France | BIOGARAN<br>15, boulevard Charles de Gaulle<br>92707 Colombes Cedex<br>France | TRIMETAZIDINE ALMUS | 20 mg | Film-coated tablet | Oral use |
| France | BIOGARAN<br>15, boulevard Charles de Gaulle<br>92707 Colombes Cedex<br>France | TRIMETAZIDINE BIOGARAN | 20 mg | Film-coated tablet | Oral use |
| France | BIOGARAN<br>15, boulevard Charles de Gaulle<br>92707 Colombes Cedex<br>France | TRIMETAZIDINE BIOGARAN | 20 mg/ml | Oral solution | Oral use |
| France | BIOGARAN<br>15, boulevard Charles de Gaulle<br>92707 Colombes Cedex<br>France | TRIMETAZIDINE BIOGARAN | 35 mg | Modified-release film-coated tablet | Oral use |
| France | CRISTERS<br>22 quai Gallieni<br>92150 Suresnes<br>France | TRIMETAZIDINE CRISTERS | 20 mg | Film-coated tablet | Oral use |
| France | QUALIMED<br>117, allée des Parcs<br>69800 Saint-Priest<br>France | TRIMETAZIDINE QUALIMED | 20 mg/ml | Oral drops, solution | Oral use |
| France | QUALIMED<br>117, allée des Parcs<br>69800 Saint-Priest<br>France | TRIMETAZIDINE QUALIMED | 35 mg | Modified-release film-coated tablet | Oral use |
| France | Les Laboratoires Servier<br>50, rue Carnot<br>92284 Suresnes cedex<br>France | VASTAREL | 20 mg | Film-coated tablet | Oral use |
| France | Les Laboratoires Servier<br>50, rue Carnot<br>92284 Suresnes cedex<br>France | VASTAREL | 20 mg/ml | Oral drops, solution | Oral use |
| France | Les Laboratoires Servier<br>50, rue Carnot<br>92284 Suresnes cedex<br>France | VASTAREL | 35 mg | Modified-release film-coated tablet | Oral use |
| France | VENIPHARM<br>4, bureaux de la Colline<br>92213 Saint-Cloud<br>France | TRANETIZ | 35 mg | Modified-release film-coated tablet | Oral use |
| France | VENIPHARM<br>4, bureaux de la Colline<br>92213 Saint-Cloud<br>France | TRIGEMAX | 35 mg | Modified-release film-coated tablet | Oral use |

| Country | Address | Name | Dosage | Form | Route |
|---|---|---|---|---|---|
| France | BIOGARAN<br>15, boulevard Charles de Gaulle<br>92707 Colombes Cedex<br>France | TRIMETAZIDINE BGR | 35 mg | Modified-release film-coated tablet | Oral use |
| France | CLL PHARMA<br>Nice Premier - Arénas<br>455, Promenade des Anglais<br>06299 Nice Cedex 03 France | TRIMETAZIDINE CLL PHARMA | 35 mg | Modified-release film-coated tablet | Oral use |
| France | SOCIÉTÉ IPSOR GENERIQUES - IGEN<br>18, avenue des Champs-Elysées<br>75008 Paris<br>France | TRIMETAZIDINE IGEN | 20 mg/ml | Oral drops, solution | Oral use |
| France | LABORATOIRES IPSOR<br>18 Avenue des Champs Elysees<br>75008 Paris<br>France | TRIMETAZIDINE IPSOR | 20 mg | Film-coated tablet | Oral use |
| France | LABORATOIRES IPSOR<br>18 Avenue des Champs Elysees<br>75008 Paris<br>France | TRIMETAZIDINE IPSOR | 20 mg/ml | Oral drops, solution | Oral use |
| France | PLUS PHARMACIE SA<br>26, boulevard Paul Vaillant-Couturier<br>94200 Ivry-sur-Seine France | TRIMETAZIDINE ISOMED | 35 mg | Modified-release film-coated tablet | Oral use |
| France | CLL PHARMA<br>Nice Premier - Arénas<br>455, Promenade des Anglais<br>06299 Nice Cedex 03 France | TRIMETAZIDINE MILGEN | 20 mg | Film-coated tablet | Oral use |
| France | CLL PHARMA<br>Nice Premier - Arénas<br>455, Promenade des Anglais<br>06299 Nice Cedex 03 France | TRIMETAZIDINE MILGEN | 20 mg/ml | Oral drops, solution | Oral use |
| France | RATIOPHARM GMBH<br>Graf Arco Strasse 3<br>89079 Ulm<br>Germany | TRIMETAZIDINE RATIOPHARM | 35 mg | Modified-release film-coated tablet | Oral use |
| France | SUBSTIPHARM<br>8, rue Bellini<br>75116 Paris<br>France | TRIMETAZIDINE SUBSTIPHARM | 20 mg/ml | Oral drops, solution | Oral use |
| France | ZYDUS FRANCE<br>25, rue des Peupliers<br>ZAC Les Hautes Pâtures - Parc d'Activités des Peupliers<br>92000 Nanterre<br>France | TRIMETAZIDINE ZYDUS | 20 mg | Film-coated tablet | Oral use |
| France | ZYDUS FRANCE<br>25, rue des Peupliers<br>ZAC Les Hautes Pâtures - Parc d'Activités des Peupliers<br>92000 Nanterre<br>France | TRIMETAZIDINE ZYDUS | 20 mg/ml | Oral solution | Oral use |
| France | VENIPHARM<br>4, bureaux de la Colline<br>92213 Saint-Cloud<br>France | TRIMEVENI | 35 mg | Modified-release film-coated tablet | Oral use |

| Country | Address | Name | Dosage | Form | Route |
|---|---|---|---|---|---|
| France | TEVA SANTE<br>Le Palatin 1<br>1 cours du Triangle<br>92936 Paris la Défense Cedex<br>France | TRIMETAZIDINE TEVA | 20 mg/ml | Oral solution | Oral use |
| France | TEVA SANTE<br>Le Palatin 1<br>1 cours du Triangle<br>92936 Paris la Défense Cedex<br>France | TRIMETAZIDINE TEVA | 20 mg | Film-coated tablet | Oral use |
| France | TEVA SANTE<br>Le Palatin 1<br>1 cours du Triangle<br>9296 Paris la Défense Cedex<br>France | TRIMETAZIDINE TEVA | 35 mg | Modified-release film-coated tablet | Oral use |
| France | SANOFI AVENTIS FRANCE<br>1-13, boulevard Romain Rolland<br>75014 Paris<br>France | TRIMETAZIDINE WINTHROP | 20 mg | Film-coated tablet | Oral use |
| France | SANOFI AVENTIS FRANCE<br>1-13, boulevard Romain Rolland<br>75014 Paris<br>France | TRIMETAZIDINE WINTHROP | 20 mg/ml | Oral solution | Oral use |
| France | SANOFI AVENTIS FRANCE<br>1-13, boulevard Romain Rolland<br>75014 Paris<br>France | TRIMETAZIDINE WINTHROP | 35 mg | Modified-release film coated tablet | Oral use |
| France | AJC INVEST<br>6, rue de la Rochefoucauld<br>16000 Angoulême<br>France | RIMETAZE | 20mg | Film coated tablet | Oral use |
| France | AJC INVEST<br>6, rue de la Rochefoucauld<br>16000 Angoulême<br>France | RIMETAZE | 20 mg/ml | Oral solution | Oral use |
| France | MYLAN SAS<br>117, allée des Parcs<br>69800 Saint-Priest<br>France | TRIMETAZIDINE MYLAN | 20 mg | Film coated tablet | Oral use |
| France | MYLAN SAS<br>117, allée des Parcs<br>69800 Saint-Priest<br>France | TRIMETAZIDINE MYLAN | 20 mg/ml | Oral solution | Oral use |
| France | MYLAN SAS<br>117, allée des Parcs<br>69800 Saint-Priest<br>France | TRIMETAZIDINE MYLAN | 35 mg | Modified-release film-coated tablet | Oral use |
| France | SANDOZ<br>49, avenue Georges Pompidou<br>92300 Levallois-Perret<br>France | TRIMETAZIDINE SANDOZ | 20 mg | Film coated tablet | Oral use |

| Country | Address | Name | Dosage | Form | Route |
|---|---|---|---|---|---|
| France | SANDOZ<br>49, avenue Georges Pompidou<br>92300 Levallois-Perret<br>France | TRIMETAZIDINE SANDOZ | 20 mg/ml | Oral solution | Oral use |
| France | ACTAVIS France<br>La Boursidière Centre d'Affaires 92357 Le Plessis Robinson<br>France | TRIMETAZIDINE ACTAVIS | 20 mg | Film coated tablet | Oral use |
| France | QUALIMED<br>117, allée des Parcs<br>69800 Saint-Priest<br>France | TRIMETAZIDINE QUALIMED | 20 mg | Film coated tablet | Oral use |
| France | PLUS PHARMACIE SA<br>26, boulevard Paul Vaillant-Couturier<br>94200 Ivry-sur-Seine<br>France | TRIMETAZIDINE ISOMED | 20 mg | Coated tablet | Oral use |
| France | EG LABO - LABORATOIRES EUROGENERICS<br>"Le Quintet" - bâtiment A<br>12, rue Danjou<br>92517 Boulogne Billancourt Cedex<br>France | TRIMETAZIDINE EG | 20 mg | Film coated tablet | Oral use |
| France | EG LABO - LABORATOIRES EUROGENERICS<br>"Le Quintet" - bâtiment A<br>12, rue Danjou<br>92517 Boulogne Billancourt Cedex<br>France | TRIMETAZIDINE EG | 20 mg/ml | Oral solution | Oral use |
| France | EG LABO - LABORATOIRES EUROGENERICS<br>"Le Quintet" - bâtiment A<br>12, rue Danjou<br>92517 Boulogne Billancourt Cedex<br>France | TRIMETAZIDINE EG | 35 mg | Modified-release film-coated tablet | Oral use |
| France | ARROW GENERIQUES<br>26, avenue Tony Garnier<br>69007 Lyon<br>France | TRIMETAZIDINE ARROW | 20 mg | Film coated tablet | Oral use |
| France | ARROW GENERIQUES<br>26, avenue Tony Garnier<br>69007 Lyon<br>France | TRIMETAZIDINE ARROW | 20 mg/ml | Oral solution | Oral use |
| France | RATIOPHARM GMBH<br>Graf Arco Strasse 3<br>89079 Ulm<br>Germany | TRIMETAZIDINE RATIOPHARM | 20 mg | Coated tablet | Oral use |
| France | RATIOPHARM GMBH<br>Graf Arco Strasse 3<br>89079 Ulm<br>Germany | TRIMETAZIDINE RATIOPHARM | 20 mg/ml | Oral solution | Oral use |

| Country | Address | Name | Dosage | Form | Route |
|---|---|---|---|---|---|
| France | SANDOZ<br>49, avenue Georges Pompidou<br>92300 Levallois-Perret<br>France | TRIMETAZIDINE SANDOZ | 35 mg | modified-release film-coated tablet | Oral use |
| Greece | HELP ABEE,<br>Valaoritou 10<br>Metamorfosi Attikis 14452<br>Greece | NOVAZIDINE | 20mg/ml | Oral drops, solution | Oral use |
| Greece | FOINIXFARM EPE<br>Dervenakion 38 & Sachini<br>Gerakas 15344<br>Greece | ZIDIN | 20mg/ml | Oral drops, solution | Oral use |
| Greece | SERVIER HELLAS PHARMACEUTICALS Ltd,<br>Ethnikis Antistaseos 72 & Agamemnonos<br>Greece | VASTAREL | 20 mg/tab | Film-coated tablet | Oral use |
| Greece | SERVIER HELLAS PHARMACEUTICALS Ltd,<br>Ethnikis Antistaseos 72 & Agamemnonos<br>Greece | VASTAREL | 20mg/ml | Oral drops, solution | Oral use |
| Greece | SERVIER HELLAS PHARMACEUTICALS Ltd,<br>Ethnikis Antistaseos 72 & Agamemnonos<br>Greece | VASTAREL | 35 mg/tab | Controlled release tablet | Oral use |
| Poland | Ethifarm Sp. z o. o.<br>ul. Hiacyntowa 39<br>60-175 Poznań<br>Poland | Cyto-Protectin MR | 35mg | Prolonged-release tablet | Oral use |
| Poland | Przedsiębiorstwo Farmaceutyczne LEK-AM Sp. z o.o.<br>Ostrzykowizna 14A<br>05-170 Zakroczym<br>Poland | Trimeductan MR | 35mg | Prolonged-release tablet | Oral use |
| Poland | Pabianickie Zakłady Farmaceutyczne Polfa S.A.<br>Marszałka J. Piłsudskiego 5,<br>95-200 Pabianice<br>Poland | Metazydyna | 20 mg | Film-coated tablet | Oral use |
| Poland | Les Laboratoires Servier,<br>50, rue Carnot<br>92284 Suresnes cedex<br>France | Preductal | 20 mg | Film-coated tablet | Oral use |
| Poland | ANPHARM Przedsiębiorstwo Farmaceutyczne S.A.<br>ul. Annopol 6B<br>03-236 Warszawa<br>Poland | Preductal MR | 35 mg | Modified-release film-coated tablet | Oral use |
| Poland | Gedeon Richter Polska Sp. z o.o.<br>Graniczna str. 35<br>05-825 Grodzisk Mazowiecki<br>Poland | Protevasc SR | 35 mg | Modified-release film-coated tablet | Oral use |
| Poland | ratiopharm GmbH<br>Graf-Arco-Strasse 3<br>Ulm, 89079<br>Germany | Trimetaratio | 20 mg | Film-coated tablet | Oral use |

| Country | Address | Name | Dosage | Form | Route |
|---|---|---|---|---|---|
| Poland | ratiopharm GmbH<br>Graf-Arco-Strasse 3<br>Ulm, 89079<br>Germany | Trimetazidine-ratiopharm PR | 35 mg | Prolonged-release tablet | Oral use |
| Poland | Ethifarm Sp. z o. o.<br>ul. Hiacyntowa 39<br>60-175 Poznań<br>Poland | Cyto-Protectin MR | 35mg | Prolonged-release tablet | Oral use |
| Poland | Glenmark Pharmaceuticals s.r.o.<br>Hvezdova 1716/2b<br>Praga 4<br>CZ-140 78<br>Czech Republic | Portora | 35 mg | Prolonged-release tablet | Oral use |
| Poland | Zentiva, k.s.<br>U kabelovny 130<br>Praga 10, Dolni Mecholupy<br>10237 Dolni Mecholupy<br>Czech Republic | Trimedal | 35 mg | Prolonged-release tablet | Oral use |
| Poland | Sandoz GmbH<br>Biochemiestrasse 10<br>A-6250 Kundl<br>Austria | Dimesar | 35 mg | Prolonged-release tablet | Oral use |
| Romania | MYLAN S.A.S.<br>117, Allée des Parcs<br>69800 Saint Priest<br>France | Trimetazidina Mylan | 35 mg | Prolonged-release tablet | Oral use |
| Romania | S.C. TERAPIA S.A.<br>Str. Fabricii nr. 124<br>Cluj Napoca<br>România | DILATAN MR 35 mg, comprimate filmate cu eliberare modificată, 35 mg | 35 mg | Prolonged-release tablet | Oral use |
| Romania | S.C. TERAPIA S.A.<br>Str. Fabricii nr. 124<br>Cluj Napoca<br>România | DILATAN 20 mg, comprimate filmate, 20 mg | 20mg | Film-coated tablet | Oral use |
| Romania | S.C. VIM SPECTRUM S.R.L.,<br>Şos. Sighişoarei nr. 409,<br>Sat Corunca, Com. Livezeni<br>Jud. Mureş<br>România | TRIMETAZIDIN VIM SPECTRUM 20 mg, capsule | 20 mg | Capsule | Oral use |
| Romania | Les Laboratoires Servier,<br>50, rue Carnot<br>92284 Suresnes cedex<br>France | PREDUCTAL MR 35 mg, comprimate filmate cu eliberare modificată | 35 mg | Modified-release tablet | Oral use |
| Romania | Les Laboratoires Servier,<br>50, rue Carnot<br>92284 Suresnes cedex<br>France | PREDUCTAL 20 mg, comprimate filmate | 20 mg | Film-coated tablet | Oral use |
| Romania | GEDEON RICHTER ROMÂNIA S. A.<br>Str. Cuza - Vodă nr. 99 – 105<br>Târgu – Mureş<br>România | MODUXIN MR 35 mg, comprimate filmate cu eliberare prelungită | 35 mg | Prolonged-release tablet | Oral use |
| Romania | GEDEON RICHTER ROMÂNIA S. A.<br>Str. Cuza - Vodă nr. 99 – 105<br>Târgu – Mureş<br>România | MODUXIN 20 mg, comprimate filmate | 20 mg | Film-coated tablet | Oral use |

| Country | Address | Name | Dosage | Form | Route |
|---|---|---|---|---|---|
| Romania | S.C. TERAPIA S.A.<br>Str. Fabricii nr. 124<br>Cluj Napoca<br>România | TRIMETAZIDINA 20 mg, drajeuri | 20 mg | Coated tablet | Oral use |
| Romania | LABORMED PHARMA S.A. Bd. Theodor Pallady nr. 44B<br>sector 3, Bucureşti<br>România | TRIMETAZIDINĂ LPH 35mg, comprimate filmate cu eliberare modificată | 35 mg | Modified-release tablet | Oral use |
| Romania | LABORMED PHARMA S.A. Bd. Theodor Pallady nr. 44B<br>sector 3, Bucureşti<br>România | TRIMETAZIDINĂ LPH 20 mg, comprimate filmate | 20 mg | Film-coated tablet | Oral use |
| Romania | LABORMED PHARMA S.A.<br>Bd. Theodor Pallady nr. 44B<br>sector 3, Bucureşti<br>România | Oxcardin 20 mg, comprimate filmate | 20 mg | Film-coated tablet | Oral use |
| Romania | LABORMED PHARMA S.A.<br>Bd. Theodor Pallady nr. 44B<br>sector 3, Bucureşti<br>România | Oxcardin MR 35mg, comprimate filmate cu eliberare modificată | 35 mg | Modified-release tablet | Oral use |
| Romania | GLENMARK PHARMACEUTICALS s.r.o.<br>Hvezdova 1716/2b, Prague 4, 140 78<br>Czech Republic | APSTAR 35 mg comprimate cu eliberare prelungită | 35 mg | Prolonged-release tablet | Oral use |
| Romania | S.C.SANDOZ S.R.L.<br>Str. Livezeni nr. 7A<br>540472 Târgu Mureş<br>România | TRIMELUZINE 35 mg comprimate cu eliberare prelungită | 35 mg | Prolonged-release tablet | Oral use |
| Spain | LABORATORIOS DAVUR, S.L.<br>C/ Teide, 4- planta baja<br>Polígono Empresarial La Marina<br>28703 San Sebastian de los Reyes (MADRID)<br>Spain | TRIMETAZIDINA DAVUR 20 mg comprimidos recubiertos EFG | 20 mg | Film-coated tablet | Oral use |
| Spain | RIMAFAR, S.L.<br>Polígono Industrial Malpica<br>Calle C, Nº 4<br>50016 ZARAGOZA<br>Spain | TRIMETAZIDINA RIMAFAR 20 mg comprimidos recubiertos EFG | 20 mg | Film-coated tablet | Oral use |
| Spain | RATIOPHARM ESPAÑA, S.A. Avda. Burgos, 16 D-5ª planta<br>28036 MADRID<br>Spain | TRIMETAZIDINA RATIOPHARM 20 mg comprimidos recubiertos con película EFG | 20 mg | Film-coated tablet | Oral use |
| Spain | DANVAL, S.A.<br>Avda. de los Madroños, 33<br>28043 Madrid<br>Spain | IDAPTAN 20 mg comprimidos recubiertos con película | 20 mg | Film-coated tablet | Oral use |
| Spain | DANVAL, S.A.<br>Avda. de los Madroños, 33<br>28043 Madrid<br>Spain | IDAPTAN 20 mg/ml solución oral | 20 mg/ml | Oral solution | Oral use |

| Country | Address | Name | Dosage | Form | Route |
|---|---|---|---|---|---|
| Spain | LABORATORIOS CINFA, S.A.<br>C/ Olaz-Chipi, 10<br>Polígono Industrial Areta<br>31620 Huarte (PAMPLONA)<br>Spain | TRIMETAZIDINA CINFA 20 mg comprimidos recubiertos con película EFG | 20 mg | Film-coated tablet | Oral use |
| Spain | PENSA PHARMA, S.A.U.<br>C/ Jorge Comín (Médico Pediatra)<br>3-bajos<br>46015 Valencia<br>Spain | TRIMETAZIDINA PENSA 20 mg comprimidos recubiertos con película EFG | 20 mg | Film-coated tablet | Oral use |

# Appendix 2: Available specialties in PI panel in each country and the definition of each specialty by country

| Analysis class | FRANCE | | SPAIN | | POLAND | | GREECE | |
|---|---|---|---|---|---|---|---|---|
| | Code | Name | Code | Name | Code | Name | Code | Name |
| GP | 1 | General practice | 1 | General practice | | | 1 | General practice |
| GP | | | 54 | Family practice | 54 | Family practice | | |
| GP | | | 2 | Internal medicine | 2 | Internal medicine | | |
| PED | 9 | Pediatric | 3 | Pediatric | 3 | Pediatric | 3 | Pediatric |
| RHEU | B | Rheumatology | 6 | Rheumatology | 6 | Rheumatology | 6 | Rheumatology |
| GE | 4 | Gastroenterology | 7 | Gastroenterology | 7 | Gastroenterology | 7 | Gastroenterology |
| CARD | 2 | Cardiology | 8 | Cardiology | 8 | Cardiology | 8 | Cardiology |
| OTHER | | | 9 | Surgery | 9 | Surgery | | |
| DERM | 3 | Dermatology | 10 | Dermatology | 10 | Dermatology | 10 | Dermatology |
| END | C | Endocrinology | 11 | Endocrinology | 11 | Endocrinology | 11 | Endocrinology |
| OPTH | 7 | Ophthalmology | 12 | Ophthalmology | 12 | Ophthalmology | | |
| GYN | 5 | Gynecology | 13 | Gynecology | 13 | Gynecology | 13 | Gynecology |
| ORL | 8 | Otorhinolaryngology | 16 | Otorhinolaryngology | 16 | Otorhinolaryngology | 16 | Otolaryngology |
| OTHER | | | 17 | Traumatology | 19 | Orthopedy | 19 | Orthopedics |
| URO | G | Urology | 18 | Urology | 18 | Urology | 18 | Urology |
| PULM | A | Pulmology | 20 | Pulmology | 20 | Pulmology | 20 | Pulmology |
| NEUR | 6 | Neurology | 21 | Neurology | 21 | Neurology | 21 | Neurology |
| PSY | F | Psychiatry | 22 | Psychiatry | 22 | Psychiatry | 22 | Psychiatry |
| OTHER | | | 15 | Odonto-stomatology | 25 | Diabetology | | |
| OTHER | | | | | 30 | Allergology | | |
| GP | D | Angio-Phlebology (GP) | | | | | | |

## Appendix 3 : Physicians Stratification criteria and comparisons with the universe in PI per country

### FRANCE

### 1. General information regarding the physicians' universe and the sample

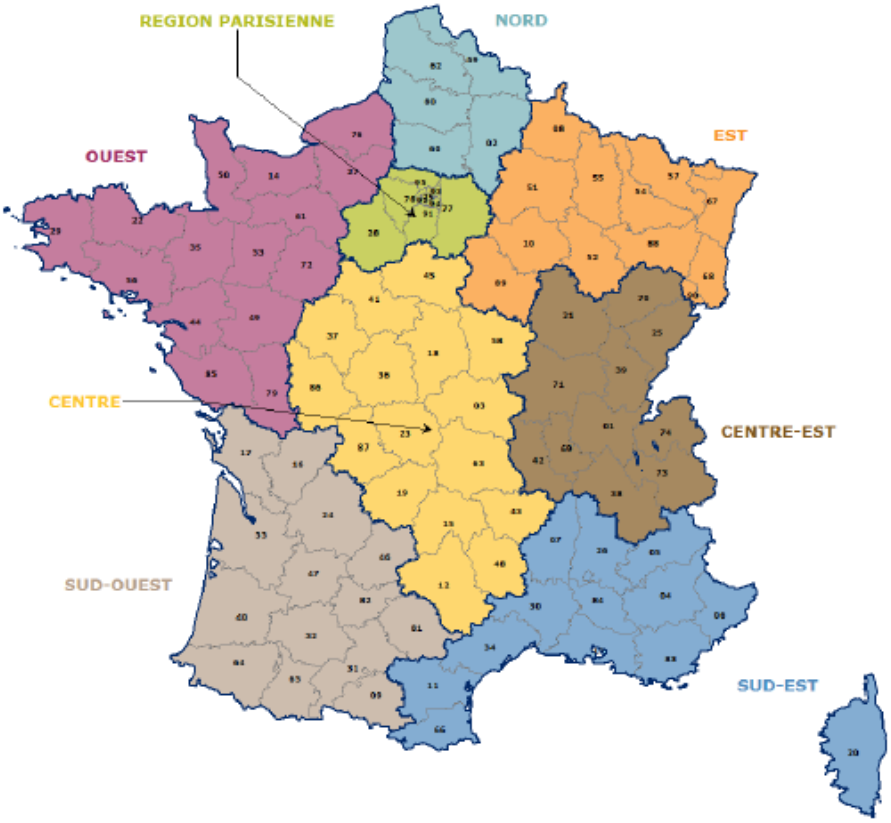
**Univers et panel – Universe & sample**
Univers / Universe: données CNAM 2010 data
Panel / Sample: conception de l'échantillon / sample design

**Specialities**: 14

| Speciality | Sample | Universe* |
|---|---|---|
| GPs | 400 | 60 974 |
| Cardiologists | 100 | 4 625 |
| Dermatologists | 80 | 3 265 |
| Endocrinologists | 40 | 960 |
| Gastroenterologists | 45 | 2 102 |
| Gynecologists | 90 | 5 458 |
| Neurologists | 40 | 806 |
| Ophthalmologists | 60 | 4 716 |
| ENT | 40 | 2 228 |
| Pediatricians | 70 | 2 730 |
| Pulmologists | 40 | 1 133 |
| Psychiatrists | 100 | 6 342 |
| Rheumatologists | 45 | 1 829 |
| Urologists | 40 | 835 |
| **Total doctors** | **1 190** | **98 003** |

**Source: CNAMTS 2010*

**Geographic**: 8 regions
1- Région parisienne
2- Nord
3- Centre
4- Ouest
5- sud-Ouest
6- Est
7- Centre-Est
8- Sud-Est




## 2. General information regarding the sample

**Sample:** 1190 physicians
From December 2011, the sample is made up of 1190 private and mixed doctors (non office-based activity below 50%) of which 400 GPs and 790 specialists in Metropolitan France.

Only the office-based practice of these physicians is collected for the study.
There is a sample turnover: the maximum time of participation is 4 consecutive years. The sample turnover is 25% per year (When 297 physicians leave the panel, 297 enter in).

**The sampling is performed using the following criteria**:
- Specialty
- Age
- Sex
- Geographic area
- Office type
- Demographic category**
- Activity score (SNIR : Système National Inter-Régimes)**

- ***Only for GPs*

**STRATIFICATION CRITERIA**: Speciality and region (listed above)

## 3. Physicians stratified by speciality and region

Spécialistes par région – Specialists by region

| Spécialités Specialists | | RP | N | O | E | C | CE | SE | SO | France |
|---|---|---|---|---|---|---|---|---|---|---|
| Cardiologues | Panel | 24 | 8 | 12 | 9 | 7 | 9 | 20 | 11 | 100 |
| Cardiologists | Univers | 1 103 | 352 | 541 | 419 | 327 | 435 | 917 | 531 | 4 625 |
| Dermatologues | Panel | 22 | 5 | 10 | 6 | 5 | 9 | 14 | 9 | 80 |
| Dermatologists | Univers | 875 | 205 | 402 | 261 | 204 | 369 | 568 | 381 | 3 265 |
| Endocrinologues | Panel | 8 | 3 | 5 | 3 | 3 | 4 | 8 | 6 | 40 |
| Endocrinologists | Univers | 226 | 50 | 130 | 49 | 62 | 102 | 196 | 145 | 960 |
| Gastro-entéro. | Panel | 10 | 4 | 6 | 4 | 3 | 5 | 8 | 5 | 45 |
| Gastro-entero. | Univers | 470 | 164 | 280 | 193 | 142 | 234 | 386 | 233 | 2 102 |
| Gynécologues | Panel | 25 | 7 | 10 | 8 | 6 | 10 | 14 | 10 | 90 |
| Gynaecologists | Univers | 1 499 | 397 | 635 | 511 | 345 | 611 | 827 | 633 | 5 458 |
| Neurologues | Panel | 8 | 3 | 5 | 3 | 3 | 6 | 7 | 5 | 40 |
| Neurologists | Univers | 166 | 59 | 103 | 66 | 52 | 114 | 142 | 104 | 806 |
| Ophtalmo. | Panel | 14 | 4 | 9 | 5 | 4 | 7 | 10 | 7 | 60 |
| Ophtalmo. | Univers | 1 149 | 309 | 685 | 379 | 327 | 521 | 810 | 536 | 4 716 |
| ORL | Panel | 10 | 3 | 5 | 3 | 3 | 4 | 7 | 5 | 40 |
| ENT | Univers | 579 | 141 | 280 | 185 | 143 | 252 | 388 | 260 | 2 228 |
| Pédiatres | Panel | 21 | 4 | 7 | 7 | 4 | 8 | 12 | 7 | 70 |
| Paediatricians | Univers | 825 | 160 | 289 | 254 | 157 | 314 | 461 | 270 | 2 730 |
| Pneumologues | Panel | 6 | 3 | 5 | 4 | 3 | 4 | 9 | 6 | 40 |
| Pulmonologists | Univers | 160 | 98 | 140 | 116 | 84 | 129 | 244 | 162 | 1 133 |
| Psychiatres | Panel | 33 | 3 | 10 | 7 | 6 | 12 | 17 | 12 | 100 |
| Psychiatrists | Univers | 2 129 | 195 | 638 | 419 | 364 | 738 | 1 072 | 787 | 6 342 |
| Rhumatologues | Panel | 10 | 3 | 6 | 4 | 3 | 6 | 8 | 5 | 45 |
| Rheumatologists | Univers | 427 | 113 | 248 | 153 | 129 | 239 | 333 | 187 | 1 829 |
| Urologues | Panel | 7 | 3 | 6 | 3 | 4 | 5 | 7 | 5 | 40 |
| Urologists | Univers | 154 | 70 | 122 | 64 | 73 | 114 | 135 | 103 | 835 |
| **Total spé.** | **Panel** | **5510** | **1105** | **2441** | **1598** | **1300** | **2346** | **3503** | **2345** | **790** |
| **Total spé.** | **Univers** | **9 762** | **2 313** | **4 493** | **3 069** | **2 409** | **4 172** | **6 479** | **4 332** | **37 029** |

## 4. General practitioners (GPs) stratified by region and type of practice

Médecins généralistes par région et activité – GPs by geography and activity score

| | Panel / Sample | | | | Univers / Universe | | | |
|---|---|---|---|---|---|---|---|---|
| Régions Regions | <3525 | [3525-5429] | >5429 | Total | <3525 | [3525-5429] | >5429 | Total |
| Reg. Parisienne | 27 | 21 | 19 | 67 | 4 189 | 3 133 | 2 853 | 10 175 |
| Nord | 8 | 10 | 20 | 38 | 1 210 | 1 543 | 3 034 | 5 787 |
| Ouest | 16 | 22 | 24 | 62 | 2 482 | 3 377 | 3 681 | 9 540 |
| Est | 10 | 13 | 15 | 38 | 1 533 | 1 910 | 2 368 | 5 811 |
| Centre | 10 | 12 | 11 | 33 | 1 488 | 1 798 | 1 647 | 4 933 |
| Centre-Est | 19 | 17 | 11 | 47 | 2 858 | 2 594 | 1 670 | 7 122 |
| Sud-est | 27 | 22 | 17 | 66 | 4 093 | 3 302 | 2 651 | 10 046 |
| Sud-ouest | 16 | 17 | 16 | 49 | 2 464 | 2 671 | 2 425 | 7 560 |
| **Total** | **133** | **134** | **133** | **400** | **20 317** | **20 328** | **20 329** | **60 974** |

## 5. General practitioners (GPs) stratified by community size/demography category

**Médecins généralistes par Habitat – GPs by demography category**

| Habitat Demography | Panel | Univers |
|---|---|---|
| <5 000 hab | 120 | 18 230 |
| [5 000 - 20 000] | 84 | 12 881 |
| [20 000 - 100 000] | 80 | 12 221 |
| > 100 000 | 49 | 7 430 |
| Paris et Banlieue | 67 | 10 212 |
| **Total** | **400** | **60 974** |

## 6. Physicians stratified by gender and age

**Médecins par sexe et par âge – Doctor by sex and age**

| Spécialités Specialists | | Femmes Women | Hommes Men | <50 ans <50 yo | 50-54 ans 50-54 yo | 55-59 ans 55-59 yo | >59 ans >59 yo | Total |
|---|---|---|---|---|---|---|---|---|
| Cardiologues | Panel | 15 | 85 | 35 | 20 | 20 | 25 | 100 |
| Cardiologists | Univers | 680 | 3 945 | 1 607 | 920 | 945 | 1 153 | 4 625 |
| Dermatologues | Panel | 51 | 29 | 21 | 19 | 21 | 19 | 80 |
| Dermatologists | Univers | 2 087 | 1 178 | 840 | 789 | 839 | 797 | 3 265 |
| Endocrinologues | Panel | 27 | 13 | 16 | 8 | 9 | 7 | 40 |
| Endocrinologists | Univers | 647 | 313 | 386 | 197 | 205 | 172 | 960 |
| Gastro-entéro. | Panel | 8 | 37 | 14 | 11 | 10 | 10 | 45 |
| Gastro-entero. | Univers | 352 | 1 750 | 681 | 502 | 452 | 467 | 2 102 |
| Gynécologues | Panel | 47 | 43 | 15 | 21 | 26 | 28 | 90 |
| Gynaecologists | Univers | 2 870 | 2 588 | 922 | 1 287 | 1 546 | 1 703 | 5 458 |
| MG | Panel | 117 | 283 | 130 | 86 | 93 | 91 | 400 |
| MG | Univers | 17895 | 43079 | 19 837 | 13 154 | 14 112 | 13 871 | 60 974 |
| Neurologues | Panel | 13 | 27 | 16 | 9 | 9 | 6 | 40 |
| Neurologists | Univers | 266 | 540 | 321 | 178 | 179 | 128 | 806 |
| Ophtalmo. | Panel | 25 | 35 | 14 | 15 | 16 | 15 | 60 |
| Ophtalmo. | Univers | 1 931 | 2 785 | 1 117 | 1 182 | 1 245 | 1 172 | 4 716 |
| ORL | Panel | 5 | 35 | 10 | 9 | 10 | 11 | 40 |
| ENT | Univers | 287 | 1 941 | 568 | 524 | 550 | 586 | 2 228 |
| Pédiatres | Panel | 38 | 32 | 15 | 15 | 16 | 24 | 70 |
| Paediatricians | Univers | 1 481 | 1 249 | 579 | 594 | 616 | 941 | 2 730 |
| Pneumologues | Panel | 9 | 31 | 11 | 10 | 11 | 8 | 40 |
| Pulmonologists | Univers | 269 | 864 | 318 | 269 | 325 | 221 | 1 133 |
| Psychiatres | Panel | 39 | 61 | 21 | 16 | 26 | 37 | 100 |
| Psychiatrists | Univers | 2 444 | 3 898 | 1 332 | 1 041 | 1 616 | 2 353 | 6 342 |
| Rhumatologues | Panel | 15 | 30 | 12 | 10 | 11 | 12 | 45 |
| Rheumatologists | Univers | 603 | 1 226 | 491 | 411 | 434 | 493 | 1 829 |
| Urologues | Panel | 1 | 39 | 21 | 7 | 6 | 6 | 40 |
| Urologists | Univers | 19 | 816 | 437 | 143 | 125 | 130 | 835 |
| **Total** | **Panel** | **410** | **780** | **351** | **256** | **284** | **299** | **1 190** |
| **Total** | **Univers** | **31 831** | **66 172** | **29 436** | **21 191** | **23 189** | **24 187** | **98 003** |

**GREECE**

## 1. General information regarding the physicians' universe and the sample

**Universe Size:** 24,967 doctors,
14 Specialties (as of Q4/2010)

***Medical Universe 2010***

| | | |
|---|---|---|
| **Speciality** | | |
| | | |
| 001 | General Practice | 1.63% |
| 003 | Paediatry | 0.93% |
| 006 | Rheumatology | 7.09% |
| 007 | Gastroenterology | 4.69% |
| 008 | Cardiology | 1.10% |
| 010 | Dermatology | 1.97% |
| 011 | Endocrinology | 3.95% |
| 013 | Gynaecology | 1.11% |
| 016 | Otorhinolaryngology | 1.74% |
| 018 | Urology | 2.22% |
| 019 | Orthopedics | 1.49% |
| 020 | Pulmology | 1.58% |
| 021 | Neurology | 1.38% |
| 022 | Psychiatry | 2.07% |
| ***Total*** | | |

**Geographic:** 7 Regions
1- Attica-Athens-Piraeus
2- Sterea
3- Peloponisus
4- Epirus
5- Thessaly
6- Macedonia/Thrace
7- Aegean Islands/Crete.


## 2. General information regarding the sample

**Sample Size:** 474 doctors (as of Q4/2011)

**Type of sample:** Random cluster sample stratified by Specialty and Region

**STRATIFICATION CRITERIA**: Speciality and region (listed above)

No available data regarding the distribution of the physicians by speciality or region for Greece.

**SPAIN**

## 1. General information regarding the physicians' universe

**Universe:** 142.967 doctors
**(as of Q1/2011)**

**Specialities analyzed separately**: 18

| COVERED | | NON - COVERED | |
|---|---|---|---|
| | DOCTORS UNIVERSE | | DOCTORS UNIVERSE |
| General Medicine (A.P.) | 22.269 | Allergy | 1.139 |
| Family Medicine (A.P.) | 30.743 | Anaesthesiology | 7.233 |
| Internal Medicine (M.I.) | 7.327 | Bacteriology | 858 |
| Endocrinology (END) | 1.649 | Geriatrics | 1.607 |
| Paediatrics (PED) | 12.407 | Haematology | 2.151 |
| Cardiology (CAR) | 3.581 | Company Medicine | 510 |
| Respiratory System (A.R.) | 2.088 | Oncology | 1.610 |
| Rheumatology (RM) | 1.177 | Radiology | 2.610 |
| Digestive System (A.D.) | 2.822 | Rehabilitation | 1.949 |
| Surgery (CIR) | 8.553 | Other Specialities | 6.058 |
| Traumatology (TR) | 6.902 | | |
| Dermatology (DR) | 2.087 | | |
| Ophthalmology (OFT) | 4.602 | | |
| Toco-Gynecology (T.GI) | 7.586 | | |
| Neurology (NL) | 2.382 | | |
| Psychiatry (PSI) | 5.798 | | |
| Odonto-Stomatology (EST) | 14.332 | | |
| Otorhinolaryngology (OTO) | 2.598 | | |
| Urology (URO) | 4.064 | | |
| **TOTAL** | **142.967** | **TOTAL** | **25.725** |

## 2. Physicians of the universe stratified by region and specialty

**UNIVERSE DESIGN FOR DOCTORS STRATIFIED BY REGION AND SPECIALTY**

| | *Speciality* | 1 | 2 | 3 | 4 | 5 | 6 | 7 | *Total* |
|---|---|---|---|---|---|---|---|---|---|
| **001** | Primary Care | **5.810** | **5.325** | **11.527** | **2.267** | **9.171** | **7.875** | **11.037** | **53.012** |
| | 001 General Practice | 2.867 | 2.107 | 4.496 | 1.059 | 3.642 | 3.143 | 4.955 | **22.269** |
| | 054 Family Practice | 2.943 | 3.218 | 7.031 | 1.208 | 5.529 | 4.732 | 6.082 | **30.743** |
| **002** | Internal Medicine | 700 | 605 | 1.864 | 235 | 1.640 | 952 | 1.331 | **7.327** |
| **003** | Pediatry | 1.055 | 1.144 | 2.917 | 401 | 2.469 | 2.006 | 2.415 | **12.407** |
| **006** | Rheumatology | 100 | 95 | 325 | 32 | 271 | 154 | 200 | **1.177** |
| **007** | Gastroenterology | 244 | 269 | 718 | 83 | 544 | 416 | 548 | **2.822** |
| **008** | Cardiology | 347 | 363 | 937 | 115 | 721 | 492 | 606 | **3.581** |
| **009** | Surgery | 967 | 850 | 2.020 | 301 | 1.681 | 1.238 | 1.496 | **8.553** |
| **010** | Dermatology | 184 | 181 | 557 | 62 | 457 | 301 | 345 | **2.087** |
| **011** | Endocrinology | 150 | 152 | 470 | 56 | 354 | 200 | 267 | **1.649** |
| **012** | Ophthalmology | 499 | 407 | 1.153 | 169 | 904 | 665 | 805 | **4.602** |
| **013** | Gynecology | 667 | 642 | 1.771 | 222 | 1.780 | 1.122 | 1.382 | **7.586** |
| **015** | Odonto-Stomatology | 1.460 | 1.496 | 3.346 | 421 | 2.644 | 2.179 | 2.786 | **14.332** |
| **016** | Otorhinolaryngology | 265 | 239 | 652 | 93 | 465 | 398 | 486 | **2.598** |
| **017** | Traumatology | 684 | 697 | 1.537 | 230 | 1.668 | 952 | 1.134 | **6.902** |
| **018** | Urology | 390 | 352 | 1.002 | 156 | 799 | 634 | 731 | **4.064** |
| **020** | Pulmology | 227 | 227 | 491 | 73 | 420 | 280 | 370 | **2.088** |
| **021** | Neurology | 218 | 259 | 640 | 78 | 540 | 327 | 320 | **2.382** |
| **022** | Psychiatry | 502 | 672 | 1.383 | 216 | 1.479 | 685 | 861 | **5.798** |
| | ***Total*** | **14.469** | **13.975** | **33.310** | **5.210** | **28.007** | **20.876** | **27.120** | **142.967** |

## 1. General information regarding the sample

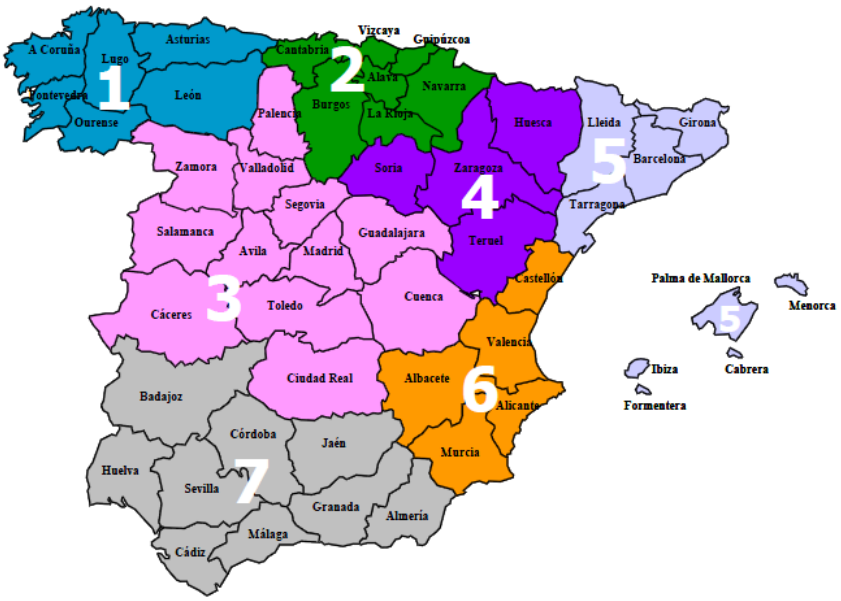
**Sample:** 935 doctors **(as of Q1/2011)**
Of which: 70% fixed and 30% rotating:
Number of Specialities analyzed separately: 18

**Type of sample**: Stratified cluster sample

**STRATIFICATION CRITERIA**:
- Proportional stratification by region and centre size.
- Disproportional stratification by speciality.

**Selection Method**: At random out of an address register arranged according to the stratification criteria.

**Regions:**
I. La Coruña, Orense, Pontevedra, Lugo, Oviedo, León.
II. Santander, Vizcaya, Alava, Guipúzcoa, Logroño, Burgos, Navarra.
III. Madrid, Toledo, Ciudad Real, Cuenca, Guadalajara, Segovia, Avila, Palencia, Zamora, Valladolid, Salamanca, Cáceres.
IV. Zaragoza, Huesca, Teruel, Soria.
V. Barcelona, Tarragona, Lérida, Gerona, Baleares.
VI. Valencia, Castellón, Alicante, Albacete, Murcia.
VII. Jaén, Almería, Granada, Málaga, Badajoz, Huelva, Cádiz, Sevilla, Córdoba.




**Community Size:**
0 - 5.000
5.001 - 30.000
30.001 - 100.000
100.001 - 1.000.000
More than 1.000.000

## 2. Physicians of the sample stratified by region and specialty

**DOCTOR PANEL STRATIFIED BY REGION AND SPECIALTY**

| *Speciality* | 1 | 2 | 3 | 4 | 5 | 6 | 7 | *Total* |
|---|---|---|---|---|---|---|---|---|
| **001** General Practice | **34** | **30** | **63** | **12** | **51** | **46** | **64** | **300** |
| 001 General Practice | 21 | 15 | 32 | 7 | 26 | 23 | 36 | **160** |
| 054 Family Practice | 13 | 15 | 31 | 5 | 25 | 23 | 28 | **140** |
| **002** Internal Medicine | 4 | 4 | 12 | 3 | 8 | 6 | 8 | **45** |
| **003** Pediatry | 6 | 6 | 14 | 3 | 13 | 11 | 12 | **65** |
| **006** Rheumatology | 3 | 2 | 8 | 1 | 7 | 4 | 5 | **30** |
| **007** Gastroenterology | 4 | 4 | 10 | 3 | 9 | 6 | 9 | **45** |
| **008** Cardiology | 4 | 5 | 10 | 3 | 9 | 6 | 8 | **45** |
| **009** Surgery | 3 | 3 | 8 | 1 | 6 | 4 | 5 | **30** |
| **010** Dermatology | 3 | 3 | 7 | 1 | 7 | 4 | 5 | **30** |
| **011** Endocrinology | 3 | 3 | 8 | 1 | 6 | 4 | 5 | **30** |
| **012** Ophthalmology | 3 | 3 | 9 | 3 | 7 | 5 | 5 | **35** |
| **013** Gynecology | 4 | 4 | 9 | 3 | 10 | 7 | 8 | **45** |
| **015** Odontology | 4 | 5 | 9 | 3 | 8 | 7 | 9 | **45** |
| **016** Otorhinolaryngology | 3 | 3 | 7 | 1 | 6 | 5 | 5 | **30** |
| **017** Traumatology | 3 | 4 | 7 | 3 | 8 | 5 | 5 | **35** |
| **018** Urology | 3 | 3 | 7 | 1 | 6 | 5 | 5 | **30** |
| **020** Pulmology | 3 | 3 | 8 | 1 | 6 | 4 | 5 | **30** |
| **021** Neurology | 3 | 3 | 8 | 1 | 7 | 4 | 4 | **30** |
| **022** Psychiatry | 3 | 4 | 8 | 1 | 10 | 4 | 5 | **35** |
| ***Total*** | **93** | **92** | **212** | **45** | **184** | **137** | **172** | **935** |

**POLAND**

## 1. General information regarding the physicians' universe

**Universe size:** 49.907 Doctors (bases on the PolishMedical Mailing Sp. z.o.o).
**(as of Q4/2005)**

**Geographic:** 3 Regions
1-Central
2-East
3-West

**Specialities:**
Family Practice
Internal Medicine
Paediatrics
Cardiology
Dermatology
Gynecology
Ophthalmology + ORL
Urology
Neurology + Psychiatry
Others (Rheumatology, Gastroenterology, Surgery, endocrinology, Orthopedy, Pulmology, Diabetology, allergology)

| | SPECIALITY |
|---|---|
| 002 | Internal Medicine |
| 054 | Familiy Practice |
| 003 | Pediatrics |
| 008 | Cardiology |
| 010 | Dermatology |
| 013 | Gynecology |
| 012 | Ophthalmology |
| 016 | Otorhinolaryngology |
| 018 | Urology |
| 021 | Neurology |
| 022 | Psychiatry |
| | Others |
| 006 | Rheumatology |
| 007 | Gastroenterology |
| 009 | Surgery |
| 011 | Endocrinology |
| 019 | Orthopedy |
| 020 | Pulmology |
| 025 | Diabetology |
| 030 | Allergology |

**SAMPLE 565** Doctors

**Type of sample:** Stratified Random Sample.
**(as of Q4/2005)**

**STRATIFICATION CRITERIA** Stratification disproportional by specialities.

**Selection method:** At random out of an address register arranged according to the stratification criteria.

**2. Physicians of the universe stratified by region and speciality**

***PLMI Universe 2005/2006***

| SPECIALITY | REGION | | | | | | | | | TOTAL | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 Central | | | 2 East | | | 3 West | | | | | |
| | InP./OutP. | OutP. | Total | InP./OutP. | OutP. | Total | InP./OutP. | OutP. | Total | InP./OutP. | OutP. | Total |
| 002 Internal Medicine | 0 | 4.071 | **4.071** | 0 | 1.652 | **1.652** | 0 | 2.944 | **2.944** | **0** | **8.667** | **8.667** |
| 054 Familiy Practice | 0 | 1.968 | **1.968** | 0 | 1.335 | **1.335** | 0 | 2.248 | **2.248** | **0** | **5.551** | **5.551** |
| 003 Pediatrics | 0 | 2.813 | **2.813** | 0 | 1.185 | **1.185** | 0 | 2.124 | **2.124** | **0** | **6.122** | **6.122** |
| 008 Cardiology | 652 | 530 | **1.182** | 244 | 87 | **331** | 328 | 270 | **598** | **1.224** | **887** | **2.111** |
| 010 Dermatology | 197 | 729 | **926** | 50 | 303 | **353** | 117 | 571 | **688** | **364** | **1.603** | **1.967** |
| 013 Gynecology | 1.204 | 1.280 | **2.484** | 522 | 458 | **980** | 942 | 1.027 | **1.969** | **2.668** | **2.765** | **5.433** |
| 012 Ophthalmology | 197 | 971 | **1.168** | 75 | 377 | **452** | 139 | 801 | **940** | **411** | **2.149** | **2.560** |
| 016 Otorhinolaryngology | 370 | 844 | **1.214** | 157 | 289 | **446** | 294 | 610 | **904** | **821** | **1.743** | **2.564** |
| 018 Urology | 287 | 127 | **414** | 90 | 28 | **118** | 187 | 75 | **262** | **564** | **230** | **794** |
| 021 Neurology | 456 | 726 | **1.182** | 244 | 256 | **500** | 298 | 503 | **801** | **998** | **1.485** | **2.483** |
| 022 Psychiatry | 284 | 551 | **835** | 133 | 220 | **353** | 230 | 407 | **637** | **647** | **1.178** | **1.825** |
| Others | | | | | | | | | | | | |
| 006 Rheumatology | 106 | 388 | **494** | 69 | 171 | **240** | 88 | 265 | **353** | **263** | **824** | **1.087** |
| 007 Gastroenterology | 197 | 154 | **351** | 63 | 36 | **99** | 94 | 57 | **151** | **354** | **247** | **601** |
| 009 Surgery | 760 | 607 | **1.367** | 364 | 211 | **575** | 629 | 537 | **1.166** | **1.753** | **1.355** | **3.108** |
| 011 Endocrinology | 144 | 181 | **325** | 70 | 63 | **133** | 79 | 118 | **197** | **293** | **362** | **655** |
| 019 Orthopedy | 554 | 337 | **891** | 236 | 81 | **317** | 370 | 191 | **561** | **1.160** | **609** | **1.769** |
| 020 Pulmology | 205 | 351 | **556** | 98 | 150 | **248** | 150 | 249 | **399** | **453** | **750** | **1.203** |
| 025 Diabetology | 177 | 195 | **372** | 66 | 66 | **132** | 91 | 111 | **202** | **334** | **372** | **706** |
| 030 Allergology | 112 | 259 | **371** | 35 | 64 | **99** | 64 | 167 | **231** | **211** | **490** | **701** |
| ***TOTAL*** | **5.902** | **17.082** | **22.984** | **2.516** | **7.032** | **9.548** | **4.100** | **13.275** | **17.375** | **12.518** | **37.389** | **49.907** |

## 3. Physicians of the sample stratified by region and speciality

***PLMI Sample Design 2005/2006***

| SPECIALITY | | REGION | | | | | | | | | TOTAL | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1 Central | | | 2 East | | | 3 West | | | | | |
| | | InP./OutP. | OutP. | Total | InP./OutP. | OutP. | Total | InP./OutP. | OutP. | Total | InP./OutP. | OutP. | Total |
| 002 | Internal Medicine | 0 | 34 | **34** | 0 | 16 | **16** | 0 | 25 | **25** | **0** | **75** | **75** |
| 054 | Familiy Practice | 0 | 12 | **12** | 0 | 9 | **9** | 0 | 14 | **14** | **0** | **35** | **35** |
| 003 | Pediatrics | 0 | 28 | **28** | 0 | 11 | **11** | 0 | 21 | **21** | **0** | **60** | **60** |
| 008 | Cardiology | 11 | 9 | **20** | 4 | 1 | **5** | 6 | 4 | **10** | **21** | **14** | **35** |
| 010 | Dermatology | 2 | 7 | **9** | 1 | 3 | **4** | 1 | 6 | **7** | **4** | **16** | **20** |
| 013 | Gynecology | 9 | 9 | **18** | 4 | 4 | **8** | 6 | 8 | **14** | **19** | **21** | **40** |
| 012 | Ophthalmology | 2 | 7 | **9** | 1 | 3 | **4** | 1 | 6 | **7** | **4** | **16** | **20** |
| 016 | Otorhinolaryngology | 4 | 8 | **12** | 1 | 3 | **4** | 3 | 6 | **9** | **8** | **17** | **25** |
| 018 | Urology | 9 | 4 | **13** | 3 | 1 | **4** | 6 | 2 | **8** | **18** | **7** | **25** |
| 021 | Neurology | 5 | 7 | **12** | 2 | 3 | **5** | 3 | 5 | **8** | **10** | **15** | **25** |
| 022 | Psychiatry | 4 | 7 | **11** | 2 | 3 | **5** | 3 | 6 | **9** | **9** | **16** | **25** |
| | Others | | | | | | | | | | | | |
| 019 | Orthopedy | 8 | 5 | **13** | 3 | 1 | **4** | 5 | 3 | **8** | **16** | **9** | **25** |
| 020 | Pulmology | 4 | 8 | **12** | 2 | 3 | **5** | 3 | 5 | **8** | **9** | **16** | **25** |
| 006 | Rheumatology | 2 | 7 | **9** | 1 | 4 | **5** | 1 | 5 | **6** | **4** | **16** | **20** |
| 007 | Gastroenterology | 8 | 7 | **15** | 2 | 2 | **4** | 4 | 2 | **6** | **14** | **11** | **25** |
| 009 | Surgery | 6 | 5 | **11** | 3 | 2 | **5** | 5 | 4 | **9** | **14** | **11** | **25** |
| 011 | Endocrinology | 4 | 6 | **10** | 2 | 2 | **4** | 2 | 4 | **6** | **8** | **12** | **20** |
| 025 | Diabetology | 5 | 6 | **11** | 1 | 2 | **3** | 3 | 3 | **6** | **9** | **11** | **20** |
| 030 | Allergology | 3 | 7 | **10** | 1 | 2 | **3** | 2 | 5 | **7** | **6** | **14** | **20** |
| | ***TOTAL*** | **86** | **183** | **269** | **33** | **75** | **108** | **54** | **134** | **188** | **173** | **392** | **565** |

## Appendix 4: Arguments in favour of fixed or rotating panels

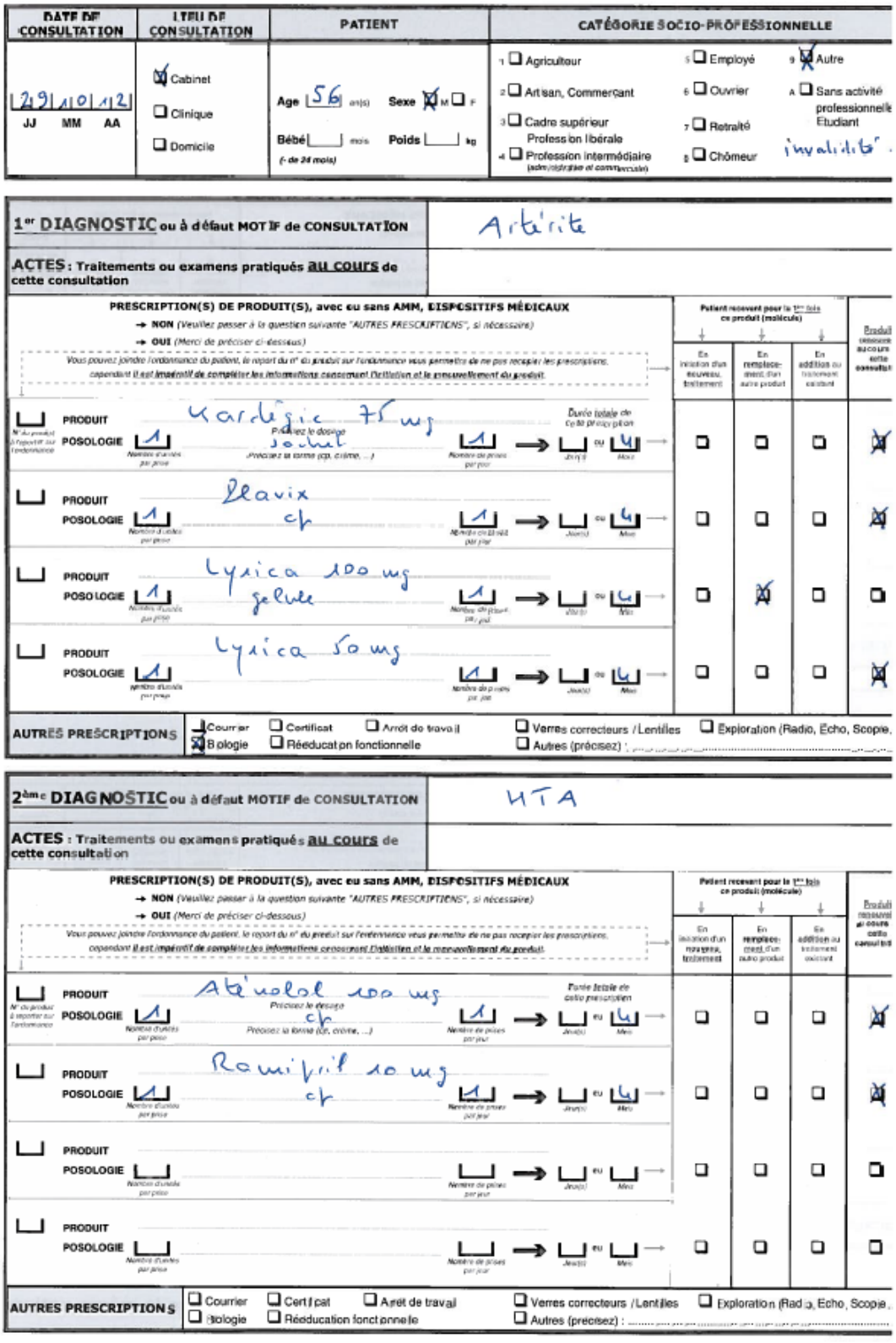
*From a statistical perspective there are arguments in favour of fixed panels as well as rotating samples:*

Pro "Fixed Panel"
Growth Rates and Data Fluctuation: constant panels produce more accurate growth rates and absolute deltas. This is due to the fact that the monthly/quarterly variances don't simply add up but the co-variance between the two periods can be deducted. In the end product, less fluctuation is shown and more stable/robust data from one cycle to another - a very important criterion when clients are assessing the quality of our data.
Panel QC: Due to the longer collaboration, IMS Health is able to better control atypical behaviour, low reporting and unusual changes. There is a learning curve during the initial cycles where IMS Health can help and feed back to the doctor how to produce more complete and valid input. On top, there is a closer relationship with our panel management which has a positive impact on the reporting behaviour.
Representativeness: Fixed panels allows for a better control of the design accomplishment. It furthermore, through quality controls, allows rejecting physicians that do not meet IMS Health quality standards in terms of reporting completeness and consistency. These factors have a positive influence on the representativeness of IMS Health medical data.
Longitudinal Analyses: fixed doctor codes are used which gives the option to run long-term analyses for panel physicians who have been within the panel for more than a year or so. This gives additional opportunities for ad-hoc data insights.

Pro "Rotating Sample"
"Panel aging": It may happen that a fixed panel loses representation of the universe as young physicians entering the universe have a lower likelihood to be part of the panel.
“Volume estimates”: Samples have a higher accuracy of volume estimates (e.g. MAT total prescriptions), as the individual quarterly samples are statistically independent and no co-variance effect has to be accounted for. Also, on a yearly basis, many more physicians will be reached as compared to a fixed sample. This also could have a positive impact on the yearly data estimates. For example, if 300 new physicians are in the panel every three months, 1200 different physicians per year will be reached out for.

In weighting the arguments in favour for either sampling system IMS Health follows a balanced approach. There is also a non-induced and natural panel turn over which occurs due to practice behaviour of physicians or the fact that they are retiring with a rapid pace in some countries like France.

## Appendix 5: Medical case-record book sample page filled-in a physician of PI panel Example from France



| DATE DE CONSULTATION | LIEU DE CONSULTATION | PATIENT | CATÉGORIE SOCIO-PROFESSIONNELLE |
|---|---|---|---|
| 29/10/12 JJ MM AA | ☒ Cabinet ☐ Clinique ☐ Domicile | Age 56 an(s) Sexe ☒ M ☐ F Bébé ___ mois (- de 24 mois) Poids ___ kg | 1 ☐ Agriculteur 2 ☐ Artisan, Commerçant 3 ☐ Cadre supérieur Profession libérale 4 ☐ Profession intermédiaire 5 ☐ Employé 6 ☐ Ouvrier 7 ☐ Retraité 8 ☐ Chômeur 9 ☒ Autre invalidité A ☐ Sans activité professionnelle Etudiant |

| | |
|---|---|
| 1er DIAGNOSTIC ou à défaut MOTIF de CONSULTATION | Artérite |
| ACTES : Traitements ou examens pratiqués au cours de cette consultation | |

PRESCRIPTION(S) DE PRODUIT(S), avec ou sans AMM, DISPOSITIFS MÉDICAUX

→ NON (Veuillez passer à la question suivante "AUTRES PRESCRIPTIONS", si nécessaire)

→ OUI (Merci de préciser ci-dessous)

Vous pouvez joindre l'ordonnance du patient, le report du n° du produit sur l'ordonnance vous permettra de ne pas recopier les prescriptions, cependant il est impératif de compléter les informations concernant l'initiation et le renouvellement du produit.

| N° du produit à reporter sur l'ordonnance | | Posologie | Durée totale de cette prescription | Patient recevant pour la 1ère fois ce produit (molécule) : En initiation d'un nouveau traitement | En remplacement d'un autre produit | En addition au traitement existant | Produit reçu au cours de cette consultation |
|---|---|---|---|---|---|---|---|
| ☐ | PRODUIT Kardégic 75 mg | POSOLOGIE 1 Nombre d'unités par prise — Précisez le dosage soluté — Précisez la forme (cp, crème, ...) — 1 Nombre de prises par jour → ___ Jour(s) ou 4 Mois | | ☐ | ☐ | ☐ | ☒ |
| ☐ | PRODUIT Plavix | POSOLOGIE 1 Nombre d'unités par prise — cp — 1 Nombre de prises par jour → ___ Jour(s) ou 4 Mois | | ☐ | ☐ | ☐ | ☒ |
| ☐ | PRODUIT Lyrica 100 mg | POSOLOGIE 1 Nombre d'unités par prise — gélule — 1 Nombre de prises par jour → ___ Jour(s) ou 4 Mois | | ☐ | ☒ | ☐ | ☐ |
| ☐ | PRODUIT Lyrica 50 mg | POSOLOGIE 1 Nombre d'unités par prise — 1 Nombre de prises par jour → ___ Jour(s) ou 4 Mois | | ☐ | ☐ | ☐ | ☒ |

AUTRES PRESCRIPTIONS: ☐ Courrier ☐ Certificat ☐ Arrêt de travail ☐ Verres correcteurs / Lentilles ☐ Exploration (Radio, Écho, Scopie, ...) ☒ Biologie ☐ Rééducation fonctionnelle ☐ Autres (précisez) : ...

| | |
|---|---|
| 2ème DIAGNOSTIC ou à défaut MOTIF de CONSULTATION | HTA |
| ACTES : Traitements ou examens pratiqués au cours de cette consultation | |

PRESCRIPTION(S) DE PRODUIT(S), avec ou sans AMM, DISPOSITIFS MÉDICAUX

→ NON (Veuillez passer à la question suivante "AUTRES PRESCRIPTIONS", si nécessaire)

→ OUI (Merci de préciser ci-dessous)

Vous pouvez joindre l'ordonnance du patient, le report du n° du produit sur l'ordonnance vous permettra de ne pas recopier les prescriptions, cependant il est impératif de compléter les informations concernant l'initiation et le renouvellement du produit.

| N° du produit à reporter sur l'ordonnance | | Posologie | Durée totale de cette prescription | Patient recevant pour la 1ère fois ce produit (molécule) : En initiation d'un nouveau traitement | En remplacement d'un autre produit | En addition au traitement existant | Produit reçu au cours de cette consultation |
|---|---|---|---|---|---|---|---|
| ☐ | PRODUIT Aténolol 100 mg | POSOLOGIE 1 Nombre d'unités par prise — Précisez le dosage cp — Précisez la forme (cp, crème, ...) — 1 Nombre de prises par jour → ___ Jour(s) ou 4 Mois | | ☐ | ☐ | ☐ | ☒ |
| ☐ | PRODUIT Ramipril 10 mg | POSOLOGIE 1 Nombre d'unités par prise — cp — 1 Nombre de prises par jour → ___ Jour(s) ou 4 Mois | | ☐ | ☐ | ☐ | ☒ |
| ☐ | PRODUIT | POSOLOGIE Nombre d'unités par prise — Nombre de prises par jour → ___ Jour(s) ou Mois | | ☐ | ☐ | ☐ | ☐ |
| ☐ | PRODUIT | POSOLOGIE Nombre d'unités par prise — Nombre de prises par jour → ___ Jour(s) ou Mois | | ☐ | ☐ | ☐ | ☐ |

AUTRES PRESCRIPTIONS: ☐ Courrier ☐ Certificat ☐ Arrêt de travail ☐ Verres correcteurs / Lentilles ☐ Exploration (Radio, Écho, Scopie, ...) ☐ Biologie ☐ Rééducation fonctionnelle ☐ Autres (précisez) : ...

## Appendix 6: Prescribing Insight – Ipad screenshot in Spain

# Appendix 7: Example of aggregated data received by IMS from the NDI database

| | A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | At | RegionNa | AT | Molecule | Reimbursement Sta | Speciality | Diagnosis | Manufacturer | Product | Str | Pack | PAge | PSex | Units<br>April - September 2013 | | |
| 2 | NDA | Romania | C01D | TRIMETAZIDINE | Reimbursed | GP | 0I25003 CHR ISCHAEM HRT DIS | SERVIER | PREDUCTAL MR | 35MG | FIL.C.TAB.MR 35MG 60 | 71 - 80 | F | 169 990 | | |
| 3 | NDA | Romania | C01D | TRIMETAZIDINE | Reimbursed | GP | 0I25003 CHR ISCHAEM HRT DIS | SERVIER | PREDUCTAL MR | 35MG | FIL.C.TAB.MR 35MG 60 | 71 - 80 | M | 83 619 | | |
| 4 | NDA | Romania | C01D | TRIMETAZIDINE | Reimbursed | GP | 0I25003 CHR ISCHAEM HRT DIS | SERVIER | PREDUCTAL MR | 35MG | FIL.C.TAB.MR 35MG 60 | 61 - 70 | F | 142 451 | | |
| 5 | NDA | Romania | C01D | TRIMETAZIDINE | Reimbursed | GP | 0I25003 CHR ISCHAEM HRT DIS | SERVIER | PREDUCTAL MR | 35MG | FIL.C.TAB.MR 35MG 60 | 61 - 70 | M | 70 756 | | |
| 6 | NDA | Romania | C01D | TRIMETAZIDINE | Reimbursed | GP | 0I25003 CHR ISCHAEM HRT DIS | SERVIER | PREDUCTAL MR | 35MG | FIL.C.TAB.MR 35MG 60 | 81 - 90 | F | 83 919 | | |
| 7 | NDA | Romania | C01D | TRIMETAZIDINE | Reimbursed | GP | 0I25003 CHR ISCHAEM HRT DIS | SERVIER | PREDUCTAL MR | 35MG | FIL.C.TAB.MR 35MG 60 | 81 - 90 | M | 43 522 | | |
| 8 | NDA | Romania | C01D | TRIMETAZIDINE | Reimbursed | GP | 0I25003 CHR ISCHAEM HRT DIS | SERVIER | PREDUCTAL MR | 35MG | FIL.C.TAB.MR 35MG 60 | 51 - 60 | F | 70 365 | | |
| 9 | NDA | Romania | C01D | TRIMETAZIDINE | Reimbursed | GP | 0I25003 CHR ISCHAEM HRT DIS | SERVIER | PREDUCTAL MR | 35MG | FIL.C.TAB.MR 35MG 60 | 51 - 60 | M | 35 253 | | |
| 10 | NDA | Romania | C01D | TRIMETAZIDINE | Reimbursed | GP | 0I25003 CHR ISCHAEM HRT DIS | SERVIER | PREDUCTAL MR | 35MG | FIL.C.TAB.MR 35MG 60 | 41 - 50 | F | 9 199 | | |
| 11 | NDA | Romania | C01D | TRIMETAZIDINE | Reimbursed | GP | 0I25003 CHR ISCHAEM HRT DIS | SERVIER | PREDUCTAL MR | 35MG | FIL.C.TAB.MR 35MG 60 | 41 - 50 | M | 6 606 | | |
| 12 | NDA | Romania | C01D | TRIMETAZIDINE | Reimbursed | GP | 0I25003 CHR ISCHAEM HRT DIS | SERVIER | PREDUCTAL MR | 35MG | FIL.C.TAB.MR 35MG 60 | 91 - 100 | F | 6 023 | | |
| 13 | NDA | Romania | C01D | TRIMETAZIDINE | Reimbursed | GP | 0I25003 CHR ISCHAEM HRT DIS | SERVIER | PREDUCTAL MR | 35MG | FIL.C.TAB.MR 35MG 60 | 91 - 100 | M | 3 558 | | |
| 14 | NDA | Romania | C01D | TRIMETAZIDINE | Reimbursed | GP | 0I25003 CHR ISCHAEM HRT DIS | SERVIER | PREDUCTAL MR | 35MG | FIL.C.TAB.MR 35MG 60 | 31 - 40 | F | 918 | | |
| 15 | NDA | Romania | C01D | TRIMETAZIDINE | Reimbursed | GP | 0I25003 CHR ISCHAEM HRT DIS | SERVIER | PREDUCTAL MR | 35MG | FIL.C.TAB.MR 35MG 60 | 31 - 40 | M | 884 | | |
| 16 | NDA | Romania | C01D | TRIMETAZIDINE | Reimbursed | GP | 0I25003 CHR ISCHAEM HRT DIS | SERVIER | PREDUCTAL MR | 35MG | FIL.C.TAB.MR 35MG 60 | 21 - 30 | M | 87 | | |
| 17 | NDA | Romania | C01D | TRIMETAZIDINE | Reimbursed | GP | 0I25003 CHR ISCHAEM HRT DIS | SERVIER | PREDUCTAL MR | 35MG | FIL.C.TAB.MR 35MG 60 | 21 - 30 | F | 56 | | |