PASS INFORMATION

Study title	**Evaluation of the Effectiveness of Risk Minimisation Measures: A Joint PASS Survey among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of Trimetazidine in Bulgaria, Czech Republic, Estonia, France, Hungary, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, and Spain**
Protocol Version identifier	Version 3.0 24 November 2014
Date of last version of protocol	18 July 2014 (Version_2.0) *"Evaluation of the Effectiveness of Risk Minimisation Measures: A Joint PASS Survey among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of Trimetazidine in Bulgaria, Czech Republic, Estonia, France, Hungary, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, and Spain"*
EU PAS Register number	Study to be registered
Active substance	Trimetazidine dihydrochloride (ATC code : C01EB15)
Medicinal product	Please refer to Annex 3; List of products for which this study is applicable
Product reference	Lupamadazine 35mg Retardtabletten, Znr 80108.00.00
Procedure number	DE/H/2652/01/DC as per C(2012)6196 Final
Marketing authorization holder (MAH) or sponsor company	Consortium of companies represented by Lupin (Europe) Limited. Kindly refer to Annex 3 for the List of Companies (and/or their Affiliates and licensors) that are part of the consortium and for the complete list of marketing authorizations of TMZ containing products which are represented by this study.
Joint PASS	Yes
Research question and objectives	Research question: The research question is whether the risk minimisation measures (DHPC and updated SmPC) were effective in: • Increasing the knowledge of physicians/HCPs about the updated safety information when prescribing TMZ • Influencing the prescribing behaviour of physicians for TMZ in indications no longer approved by the Competent Authorities Primary objective: • to evaluate the proportion of targeted physicians who received, understood and agreed to implement the updated information about TMZ provided in the DHPC Secondary objectives: • to evaluate the proportions of prescriptions within the licensed indication after the update of the SmPC • to evaluate characteristics of prescribing conditions in terms of patient characteristics (age, gender) and prescription information (form of administration, dosage, new or repeat prescription, planned duration of usage, treatment situation, reason for choosing TMZ, discontinuation plan for patients already on TMZ).

Countries of study	Bulgaria, Czech Republic, Estonia, France, Hungary, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, and Spain
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Title: Evaluation of the Effectiveness of Risk Minimisation Measures: A Joint PASS Survey among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of Trimetazidine in Bulgaria, Czech Republic, Estonia, France, Hungary, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, and Spain

Sponsor:

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
AR	Adverse reaction
ASOCS	Association of Opinion and Behaviour in health field research companies
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
DHPC	Direct healthcare professional communication
EMA	European Medicines Agency
ENT	Ear/Nose/Throat
EphMRA	European Pharmaceutical Marketing Research Association
GVP	Good pharmacovigilance practices
GP	General practitioner
HCP	Health care professional
IR	Immediate release
MAH	Marketing authorization holder
MR	Modified release
PASS	Post-authorization safety study
PIL	Patient information leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
RMM	Risk minimization measures
RMP	Risk minimization plan
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SOP	Standard operating procedures
SmPC	Summary of product characteristics
STROBE	Strengthening the reporting of observational studies in epidemiology
TMZ	Trimetazidine

3. RESPONSIBLE PARTIES

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4. ABSTRACT

4.1 Title:

Evaluation of the Effectiveness of Risk Minimisation Measures: A Joint PASS Survey among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of Trimetazidine in Bulgaria, Czech Republic, Estonia, France, Hungary, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, and Spain

Main author: Dorothea von Bredow, PhD, Project Manager, IMS RWES Germany

4.2 Rationale and background

TMZ-containing medicinal products were indicated in EU for various cardiology, ophthalmology and otolaryngology indications.

Otolaryngology and ophthalmology indications included:

i. Ancillary symptomatic treatment of vertigo and tinnitus and

ii. Ancillary treatment of visual acuity decrease and visual field disturbances due to vascular reasons

On 22 April 2011, France had requested the Committee for Medicinal Products for Human Use (CHMP) to give its opinion under Article 31 of Directive 2001/83/EC on whether the marketing authorisation for TMZ-containing medicinal products will be maintained, varied, suspended or withdrawn.

The review conducted by the CHMP concluded that the evidence of the efficacy and safety in the ophthalmology and otolaryngology indications, initially suggested by the studies on the basis of multiple assessments was considered weak due to the methodology applied to the investigation and was no longer recommended since September 2012 (3).

Potential prescribers were informed of this change in the indication of TMZ through “Direct Healthcare Professional Communications” (DHPCs) and other appropriate notifications.

The survey presented here is designed to evaluate the effectiveness of these risk minimization measures (RMM). Knowledge, attitude and behaviour of the physicians in the targeted countries about the content of the DHPC and the updated SMPC are evaluated. Furthermore, the proportion of prescriptions within the licensed indication and the prescribing conditions will be analyzed. In a parallel protocol, a drug utilization study will be conducted in which the effect of the restriction on the use of TMZ will be assessed.

4.3 Research question and objectives

Research question:

The research question is whether the risk minimisation measures (DHPC and updated SmPC) were effective in:

- Increasing the knowledge of physicians/HCPs about the updated safety information when prescribing TMZ
- Influencing the prescribing behaviour of physicians for TMZ in indications no longer approved by the Competent Authorities

Primary objective:

- to evaluate the proportion of targeted physicians who received, understood and agreed to implement the updated information about TMZ provided in the DHPC

Secondary objectives:

- to evaluate the proportions of prescriptions within the licensed indication after the update of the SmPC
- to evaluate prescribing conditions in terms of patient characteristics (age, gender) and prescription information (form of administration, dosage, new or repeat prescription, planned duration of usage, treatment situation, reason for choosing TMZ, discontinuation plan for patients already on TMZ).

4.4 Study design

This is a multinational, cross-sectional, non-interventional and anonymous survey carried out among physicians. It will be conducted through a web-questionnaire among prescribers and potential prescribers of TMZ in the 12 countries where TMZ is being commercialized (Bulgaria, Czech Republic, Estonia, France, Hungary, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, and Spain).

4.5 Population

Inclusion criteria:

- Physicians prescribers, or potential prescribers, of TMZ
  - ENT-specialists,
  - ophthalmologists
  - cardiologists
  - others (GPs, internists, geriatricians)

Exclusion criteria:

- Physicians who do not treat patients or who may have a conflict of interest (i.e. physicians employed by regulatory bodies or pharmaceutical industries),
- Physicians who do not know TMZ

4.6 Variables

The collected information includes:

- Physician related data:
  - Knowledge of the physicians about the licensed use of TMZ
    - demographics
    - type of practice
    - awareness and knowledge of the safety information about TMZ presented in the updated SmPC and the DHPC
    - source of knowledge
    - physician's intention to consider the safety warnings

- Drug utilization data:
    - age, gender of patient
    - indication for which TMZ was prescribed
    - form of administration (immediate/ modified release tablet, oral solution) and dosage
    - new or repeat prescription
    - planned duration of usage
    - treatment situation (add-on, switch, reason for switch, first line therapy, other)
    - reason for choosing TMZ
    - discontinuation plan for patients already on TMZ

4.7 Data sources

The survey will collect data from the following data sources:

- Physicians files (IMS Medical Radar files) for gender, specialty and region,

- Data collected through a web questionnaire, including
    - aggregated prescription data
    - general questions about prescription habits of the participating physicians

4.8 Study size

The sample size calculation is based on the survey objective, *i.e*. to evaluate the prescribers and potential prescriber awareness of the updated safety information about TMZ in the DHPC and the updated SmPC.

For a confidence interval of 95% and a precision of 2.7%, a total of 1320 analyzable web-questionnaires will be needed for the overall sample in the twelve countries participating in the survey.

4.9 Data analysis

All analysis will be descriptive in nature and no statistical comparison will be done in this study. Results will be presented overall, by country and per specialty.

Quantitative data will be summarized descriptively using n, mean, median, standard deviation, minimum and maximum. Categorical data will be summarized using frequency and percentage. 95% confidence interval (Wald's) may be constructed around the percentage values for some variables. Some of the variables may also be summarized by country.

The proportion of targeted physicians who received, understood and agreed to implement the updated information about TMZ provided in the DHPC will be calculated.

All variables will be analyzed in total and separately for ophthalmologists, ENT specialists, cardiologists and others based on the information provided.

In a first step, calculations will be performed on raw data.

In a second step, the results will be weighted according to the real proportion of physicians in each country in order to accurately reflect the population that the survey seeks to measure.

For each country, the results will be reported according to the prescribers' specialty distributed proportionally to their weight within the IMS Medical Radar reference lists.

Possible selection bias will be assessed by comparing the distributions of available characteristics (e.g. region, age, gender, type of practice and specialty) between respondent and non-respondent physicians.

4.10 Milestones

- Start of data collection - Fieldwork: 20 November 2014
- End of data collection - Fieldwork: 20 December 2014
- Final report of study results: 31 March 2015.

5. AMENDMENTS AND UPDATES:

A previous version was submitted entitled “A cross-sectional, multi-national survey to investigate the unlicensed use of Trimetazidine (TMZ) for various Ophthalmology and Otolaryngology indications.” 05 September 2013 (Draft_1.0)

The current protocol is a thouroughly revised version based on PRAC comments.

6. MILESTONES

- Start of data collection: 20 November 2014
- End of data collection: 20 December 2014
- Final report of study results: 31 March 2015.

7. RATIONALE AND BACKGROUND

Three pharmaceutical forms of TMZ- containing medicinal products are available in EU: 20 mg tablet, 20 mg/ml oral solution and 35 mg modified release (MR) tablet.

TMZ-containing medicinal products were indicated in EU for various cardiology, ophthalmology and otolaryngology indications.

Otolaryngology and ophthalmology indications included:

- Ancillary symptomatic treatment of vertigo and tinnitus and
- Ancillary treatment of visual acuity decrease and visual field disturbances due to vascular reasons

The indication in otology was authorized in 12 European Union Member States. The recommended dosage of TMZ 20 mg was one tablet three times a day, i.e. a daily dose of 60 mg. The equivalent dosage of TMZ 35 mg is one tablet in the morning and one tablet in the evening at mealtimes, i.e. a daily dose of 70 mg.

TMZ was indicated in ophthalmology in 7 countries in the European Union. In all countries, the recommended dosage of TMZ 20 mg is one tablet three times daily, i.e. a daily dose of 60 mg and the equivalent dosage of TMZ 35 mg is one tablet morning and evening, i.e. a daily dose of 70 mg (1).

Medicines containing TMZ are being marketed in Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovakia, Slovenia and Spain (2)

On 22 April 2011, France had requested the Committee for Medicinal Products for Human Use (CHMP) to give its opinion under Article 31 of Directive 2001/83/EC on whether the marketing authorisation for TMZ-containing medicinal products will be maintained, varied, suspended or withdrawn.

The review conducted by the CHMP concluded that the evidence of the efficacy and safety in the ophthalmology and otolaryngology indications, initially suggested by the studies on the basis of multiple assessments was considered weak due to the methodology applied to the investigation and was no longer recommended since September 2012 (3).

Potential prescribers were informed of this change in the indication of TMZ through “Direct Healthcare Professional Communications” (DHPCs) and other appropriate notifications. A drug utilization study to monitor the compliance of prescribers regarding the restricted use of TMZ in ophthalmology and otolaryngology indications has been requested by the CHMP.

The analysis of the database generated from the current study will help in planning and executing appropriate risk minimization measures to be taken. The survey presented here is designed to evaluate the knowledge, attitude and behaviour of the physicians in the targeted countries about the content of the DHPC and the updated SMPC. In a parallel protocol, a drug utilization study will be conducted in which the effect of the restriction on the use of TMZ will be assessed.

7.1 RATIONALE FOR COUNTRY SELECTION

The selection of the countries to be involved in the survey was done in order to meet all the following criteria:

- European countries in which TMZ is currently registered and marketed: Bulgaria, Czech Republic, Estonia, France, Hungary, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, and Spain and
- European countries in which the physicians were targeted for the DHPC.

The survey will be conducted in the twelve following countries: Bulgaria, Czech Republic, Estonia, France, Hungary, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, and Spain.

7.2 RATIONALE FOR THE SELECTION OF THE SPECIALTIES

The MAHs are required to conduct a study to monitor the effectiveness of the DHPC in order to strengthen risk minimization measures for TMZ.

The survey will be conducted among the following specialists who were targeted for the DHPC:

- ENT-specialists,
- ophthalmologists
- cardiologists
- others (GPs, internists, geriatricians)

8. RESEARCH QUESTION AND OBJECTIVES

8.1 RESEARCH QUESTION

Research question:

The research question is whether the risk minimisation measures (DHPC and updated SmPC) were effective in:

- Increasing the knowledge of physicians/HCPs about the updated safety information when prescribing TMZ
- Influencing the prescribing behaviour of physicians for TMZ in indications no longer approved by the Competent Authorities

8.2 OBJECTIVE

Primary objective:

- to evaluate the proportion of targeted physicians who received, understood and agreed to implement the updated information about TMZ provided in the DHPC

Secondary objectives:

- to evaluate the proportions of prescriptions within the licensed indication after the update of the SmPC
- to evaluate characteristics of prescribing conditions in terms of patient characteristics (age, gender) and prescription information (form of administration, dosage, new or repeat prescription, planned duration of usage, treatment situation, reason for choosing TMZ, discontinuation plan for patients already on TMZ).

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a multi-national, cross-sectional, non-interventional and anonymous web-based survey carried out among physicians.

9.2 SETTING

The survey will be conducted among prescribers, or potential prescribers, of TMZ in the selected countries (Bulgaria, Czech Republic, Estonia, France, Hungary, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, and Spain).

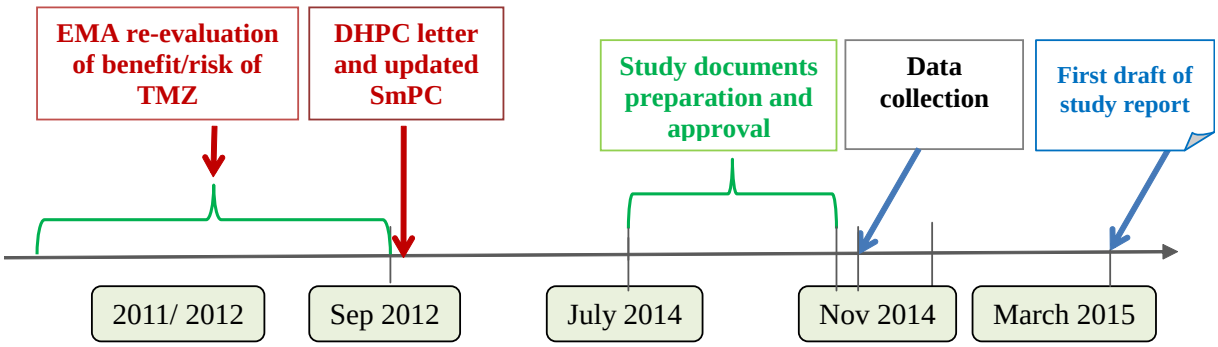

Figure 1: Study scheme and main timelines

9.2.1 Inclusion criteria

The survey will be conducted among physicians meeting the following inclusion criteria:

- Prescribers, or potential prescribers, of TMZ, i.e. physicians who know the drug,
- Specialists of any of those targeted for the DHPC:
  - ENT-specialists,
  - ophthalmologists
  - cardiologists
  - others (GPs, internists, geriatricians)

9.2.2 Exclusion criteria

Inactive and retired physicians (when documented information is available to identify them) will be deleted from the contact lists before randomisation.

The following exclusion criteria will be checked at the beginning of the web-questionnaire:

- Physicians who do not treat patients or who may have a conflict of interest (i.e. physicians employed by regulatory bodies or pharmaceutical industries),
- Physicians who do not know TMZ

9.3 VARIABLES

In this study, both physician related data about their knowledge and prescribing attitude for TMZ and drug utilization data will be collected.

Physician related data include:

- demographics
- type of practice
- knowledge of the physicians about the licensed use of TMZ
  - awareness and knowledge of the safety information about TMZ presented in the DHPC and in the updated SmPC
  - sources of knowledge
- physician's intention to consider the safety warnings

The following drug utilization data will be collected:

- age, gender of patient
- indication for which TMZ was prescribed
- form of administration (immediate/ modified release tablet, oral solution) and dosage
- new or repeat prescription
- planned duration of usage
- treatment situation (add-on, switch, reason for switch, first line therapy, other)
- reason for choosing TMZ
- discontinuation plan for patients already on TMZ

9.4 DATA SOURCES

The survey will collect data from the following sources:

- physicians files (IMS Medical Radar files)
- information collected by a web questionnaire, including
  - aggregated patient data
  - general questions about prescription habits of the participating physicians

The questionnaire will be designed by experienced persons and will include both open and close ended questions. The web questionnaire completion is estimated to take 10 to 15 minutes for the general part and an additional 5 minutes per patient for the drug utilization data. Before being finalized, the questionnaire will be administered to/ tested by 6-8 physicians in order to make sure it is well understood and the wording appropriate to the survey topic. Physicians' comments will be implemented in the final version. Moreover, the questionnaire will be translated using the back and forth method (translation from English to local language, then again to English) to make sure the appropriate wording is used.

9.5 STUDY SIZE

9.5.1 Sampling plan

The statistical unit is the physician. For each selected country, the sample survey will combine physicians recruited from two data sources:

- IMS Medical Radar's reference lists of required specialists.

For the drug utilization data, the statistical unit is the prescription.

These lists will be restricted to the targeted specialists' population, i.e. selected specialists who are currently active and not retired in 2014 at the time of the survey.
As per sample size defined below and the number of selected countries and specialities, physicians will be stratified only by country and specialty. Thereby some specialties will be combined, resulting in 4 groups of physicians:

- ENTs
- ophthalmologists
- cardiologists
- others (GPs, internists, geriatricians).

Other criteria such as region, age and gender of the prescriber are less relevant than country and specialty, since they may not be available in all countries or not be a determinant as important as country or specialty.

A random stratified sampling method will be applied. As a first step, all lists will be merged, and then the eligible physicians will be divided into homogeneous groups, called strata, which are mutually

exclusive (a physician can only belong to one stratum). This stratification will be done based on the following criteria:

- Country: 12 possibilities,
- Specialty: 4 possibilities.

Physicians are not evenly distributed across these specialties. Specialties/ groups could be combined if needed. Thus, up to 12 x 4 = 48 strata will be formed.

Table 1: Strata definition

Stratum ID	Country	Specialty
1	Bulgaria	ENT-specialists,
2		ophthalmologists
3		cardiologists
4		GPs, internists, geriatricians
5	Czech Republic	ENT-specialists,
6		ophthalmologists
7		cardiologists
8		GPs, internists, geriatricians
9	Estonia	ENT-specialists,
10		ophthalmologists
11		cardiologists
12		GPs, internists, geriatricians
13	Country 4-12	*repeat as above*

9.5.2 Study size calculation

The sample size formula based on the normal approximation to the binomial is the following :

$$n = \frac{P \cdot (1-P) \cdot \left(Z_{1-\alpha/2}\right)^2}{e^2},$$

Where *P* is the expected proportion, *e* is one half the desired width of the confidence interval, and $Z_{1-\alpha/2}$ is the standard normal *Z* value corresponding to a cumulative probability of 1 – α/2 (e.g., if α = .05 then Z = 1.96. As p is not known in advance, we consider it to be 50%. Such a hypothesis yields the most conservative i.e. largest sample size. If we consider a 2.7% precision and 95% confidence interval, we will need 1316 completed questionnaires.

For the conduct of survey, ideally the sample of 1316 physicians should be proportionally split between the selected countries based on the number of physicians in each country. However, due to large variance of the number of HCPs in targeted countries such a distribution would yield a too small number of interviews in smaller countries and would not allow the applicability of common statistical methods in those countries.

An empiric split of will be therefore implemented (

Table 2). Such sample will necessitate that the results of the study be weighted back according to the real proportion of physicians from IMS reference lists or available public information obtained through sources such as Eurostat (4) to order to allow the representativeness of the overall sample.

Usually, to ensure the robustness of statistical estimations at a given level of analysis (e.g. specialty or aggregated specialties per country), the sample size should not be lower than a threshold of 40 statistical units in each entity of this level. For analysis, less common specialties may need to be grouped. Subsequently, it will be necessary to weight back the study results according to the real proportion of physicians in order to determine the representativeness of the overall sample. In the event that the threshold of 40 statistical units (physicians per specialty in a country) would not be reached, then additional physicians of other groups will be recruited to compensate and preserve the sample size at country level.

Based on IMS Medical Radar experience from previous similar surveys and estimates, about 10-15% of physicians will not complete the questionnaire because they do not know TMZ (the questions on prescribing conditions would not be applicable to them) or because they have to interrupt the interview due to an emergency (rare). Taking this into account, recruitment of physicians should continue until 1320 analyzable questionnaires have been reached.

Table 2: Number of analyzable physician interviews required per country

Country	Sample size objective
Bulgaria	100
Czech Republic	80
Estonia	80
France	160
Hungary	100
Latvia	80

Lithuania	100
Poland	120
Portugal	150
Romania	100
Slovakia	100
Spain	150
Total Sample Size	**1320**

Sample adjustment:

Since the relative weight of each country and of each specialty in the sampling plan is different from its real relative weight in the target lists, the extrapolation of the raw survey results to the overall target population would not be relevant.

A sample adjustment will be performed. The survey results will be weighted to reflect the real proportion of the two countries and within each country to reflect the real proportion of each specialty in order to extend the survey results to the overall target population. Both unweighted (i.e. raw data) and weighted results will be presented in the report.
A weight variable will be applied to each statistical unit (i.e. the analyzable physician) during the results calculation in order to correct any over-or under-sampling that may have occurred for a country or specialty. This weight variable will indicate how many unit(s) of the population of interest an observation will count in a statistical procedure. Its value will change per country and per specialty. The weights will be normalized to obtain their sum equal to the sample size.

In order to fill-in each stratum of the sample survey from the external list and the IMS Medical Radar file, an independent sample will be selected per stratum through a simple random sampling without replacement.

In each specific stratum, physicians will be contacted according to the order of draw in this stratum. If a physician does not want to participate in the survey, the next one in order of draw will be contacted, and so on until the required number of physicians is met. If the target for a stratum is not achieved after the end of the initial list, an additional randomly sampled list will be prepared and the physicians contacted until the goal is reached or no names are left in that stratum. If the complete list of the IMS Medical Radar file has been exhausted in any particular stratum, a strategy will be determined to adjust the sample size within stratum with associated weighting.

It is to be noted that this sample is calculated to be representative as a whole (including all countries), not per country or specialty. Thus the subgroup analyses will not guarantee the same confidence intervals as the whole sample.

9.6 DATA MANAGEMENT

The survey will be conducted according to the Standard Operating Procedures (SOPs) of IMS Medical Radar and IMS Real World Evidence Solutions.

Collected data will be entered and stored in a database specific to the survey and the country. A study database will be created by merging of databases of each country.

Data will be checked in terms of consistency before data analysis:

- removal of duplicates (if required),
- data labelling and data formatting,
- range and consistency checks for each variable to identify potential non admissible values,

- cross-check the consistency of data for related variables (if feasible).

The numbers of items with missing values will be indicated. Missing values are excluded from the calculation of the percentages. The study database will be locked after validation has been completed.

9.6.1 **Data collection**

The data collection period will last about 4 weeks in November 2014, and will be conducted in parallel in the twelve countries.

The survey will be conducted by IMS Medical Radar, a division of IMS Health specialized in the conduct of phone and web surveys for more than 20 years. IMS Medical Radar will create a web-based instance survey. The lists of physicians will be loaded into separate databases for the management of the survey.

As described previously (§9.5.1: Sampling plan and §9.5.2: Study size calculation), physicians will be randomly contacted, mainly by email and also by phone when needed, according to their stratum by the IMS Medical Radar team. Their recruitment will be done as follows:

- Physicians will be invited to participate in the survey (via phone calls or mails/emails). The survey background and objectives, the contact information for questions, and the proposed compensation will be explained to the physicians at this step. If they agree to participate in the survey, they will receive a link to access the survey and the instructions for the web-questionnaire completion.
- If the questionnaire is not completed and sent to IMS Medical Radar, the physicians will be sent a reminder by email one week after the start of the survey.
- If the target is not achieved in the stratum, a reminder by phone will be conducted 1.5 weeks after the start of the survey.
- If the questionnaire is still not completed and sent to IMS Medical Radar, the physicians will be sent a last reminder by email two weeks after the start of the survey.

If necessary, the recruitment will be performed by phone to achieve the target in a specific stratum.

A physician will be considered as contacted if he/she has:

- completed the survey and sent it back to IMS Medical Radar,
- refused to participate,
- was tentatively reached out to at least 5 times.

Moreover, a physician will be considered as unreachable if he/she has been contacted at least five times without any answer.

For each physician of the sample file, the number of contacts, and the date and time when he/she completed the web questionnaire will be recorded. The recruitments in each stratum will be stopped when the target is reached. If both physician lists have been exhausted in any particular stratum, the recruitments in this stratum will be prematurely ended and a strategy will be determined to adjust the sample size with associated weighting.

9.6.2 **Approaches for increasing the response rate**

Physicians are increasingly contacted to participate in web or phone surveys. Their overall response rate of participation remains low according to international studies (5)(6)(7). Holbrook et al. showed that the response rate to surveys continues to decline over time, but a lower rate does not appear to reduce the representativeness of a demographic survey (7). VanGeest et al. conducted a systematic review of 66 published reports on efforts to perform for improving response rates (8). Two general strategies were explored: incentives-based approaches and survey design-based approaches. Financial incentives, even little ones, were effective in improving physician response rates while non-monetary

incentives were much less effective. These measures include the use of a short questionnaire, and questionnaires personalized, and approved by professional associations.

In order to increase the response rate, three actions will be applied to this survey:

- A compensation fee will be proposed to physicians for their participation in the survey.
- All physicians will be sent an email or contacted by experienced operators of IMS Medical Radar with extensive experience in conducting health related surveys.
- Each physician will be emailed or called up to 3-5 times before being considered as "not reachable", and reminders will be sent by email if IMS Medical Radar does not receive the web questionnaire.

9.7 DATA ANALYSIS

9.7.1 General statistical consideration

The statistical analysis will be conducted using the SAS® softwareV9.3 on Windows™ (SAS Institute, North Carolina, USA).

The statistical results of the twelve countries will be presented in the same report, overall, by country and per physician's specialty group.

Table 3: Mock table to implement in the statistical and study reports

				Question 1…		
Country	**ENT specialists**	**Ophthalmo-logists**	**Cardio-logists**	**Others (GPs, internists, geriatricians)**	**All (unweighted)**	**All (weighted)**
Bulgaria	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xxx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Czech Republic	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Estonia	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Etc, for all participating countries						

Overall - unweighted results	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xxx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Overall - weighted results	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xx)	(N=xxx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: The table structure may be adjusted in the final study report.

All the analysis will be descriptive in nature and no statistical comparison will be done in this study.

Quantitative data will be summarized descriptively using n, mean, median, standard deviation, minimum and maximum. Categorical data will be summarized using frequency and percentage. 95% confidence interval (Wald's) may be constructed around the percentage values for some variables. Some of the variables may also be summarized by country.

Analysis for primary objective:

The proportion of targeted physicians who received, understood and agreed to implement the updated information about TMZ provided in the DHPC will be calculated. Analysis will be done in total and separately by specialty (ophthalmologists, ENT-specialists, cardiologists and others) using proportions and the corresponding 95% Wald confidence intervals).

Analysis for the secondary objectives:

The following variables will be analyzed separately for ophthalmologists, ENT specialists, cardiologists and others based on the information provided:

- proportion of prescriptions with the licensed indication will be summarized
- characteristics (age, gender) of patients to whom TMZ is prescribed will be summarized categorically.
- Data on type of TMZ prescribed (IR/MR/Oral Solution) will be summarized through frequencies and percentages.
- Proportion of cases where TMZ was prescribed as a combination / add-on treatment will be summarized through frequencies and percentages.
- Reasons for prescribing TMZ over other drugs will be summarized categorically.
- Timeframe to keep patient on TMZ will be summarized categorically.
- Discontinuation plan for the patients already on TMZ will be listed.

In a first step, calculations will be performed on raw data. No projection factor will be applied to generalize the results to the entire prescribers' universe. As a consequence, the line "Overall – unweighted results" will show only the results observed on the overall sample, and will not reflect the

countries' universe since this sample is not proportional to the size of the external list of physicians or IMS Medical Radar reference files in each country.

In a second step, the results will be weighted according to the real proportion of physicians in each country in order to accurately reflect the population that the survey seeks to measure.

For each country, the results will be reported according to the prescribers' specialty distributed proportionally to their weight within the IMS Medical Radar reference lists.

Possible selection bias will be assessed by comparing the distributions of available characteristics (e.g. region, age, gender, type of practice and specialty) between respondent and non-respondent physicians.

Handling of missing data:
The number of missing data will be indicated. Missing data will not be replaced by imputation methods. They are expected to be few and distributed at random.

9.7.2 **Analysis of non-participation or refusal to participate rate**

As often required by the Authorities, the following different cases of total non-response will be distinguished and analyzed:

- Targeted physicians: Physicians reached to whom an email or mail has been sent, or have been called.
- Contacted physicians: Physicians who have been reached out by phone or have opened their email (if the score is technically available in their country).
- Physicians who agreed to participate: Physicians willing to participate in the survey (e.g. by phone or by clicking on the link provided in the recruitment email).
- Physicians with complete questionnaire: Physicians who actually completed the questionnaire until its end**.**

The physicians' participation in the survey will be examined via different ratios:

- Contact rate = contacted physicians / targeted physicians
- Response rate = Physicians who agreed to participate/ contacted physicians
- Cooperation rate = Physicians with complete questionnaire / Physicians who agreed to participate
- Refusal rate = contacted physicians-physicians who agreed to participate / Physicians reached

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 results validity, as recommended by the STROBE guidelines (9).

9.7.3 **Questionnaire analysis**

The general statistical considerations described above (§9.7.1) will be applied for quantitative and qualitative variables. The number of missing data will be indicated. Missing values are expected to be few and distributed at random. Since there is no applicable method unanimously accepted, there will be no replacement or imputation of missing data (10).

Confidence intervals of 95% will be calculated for variables.

Physicians' answers will be analysed by subgroups of physician's specialty per country, and on the overall dataset.

9.8 QUALITY CONTROL

9.8.1 Approaches for validating the questionnaire

The questionnaire will be tested among 5-6 physicians for its comprehensibility, consistency and the appropriateness of medical terms. The questionnaire will be translated into local languages using the back and forth method (translation from English to local language, then again to English) to ensure correct translation and that appropriate wording is used.

9.8.2 Approaches for validating the results

The quality control for validating the results will be conducted at five levels:

1) At IMS Medical Radar management level, every efforts will be undertaken to collect complete and valid data:
    - Verification of the reliability and security of the web-questionnaire interface by a qualified web-master for each country,
    - Monitoring of the quality and datasets definition by a qualified data manager. In the background of the web-questionnaire, real-time checks of the answers provided by the respondents will be developed. Non admissible answers (i.e. incorrect or unusual values, outlying values) will be detected and queries sent to the physician.
2) At the study database level (after merging datasets of each country), final data quality checks will be applied (beyond data management process):
    - Distribution of each variable in order to count the number of missing values and estimate the associated relative percentage,
    - Identification and count of non-analyzable questionnaires:
        - estimation of the percentage of physicians who do not know TMZ
        - estimation of the percentage of physicians without complete analyzable questionnaire.

Any changes in the database will be tracked and documented. The country-datasets will be stored in a dedicated database. After data have been validated and quality checked, the database will be locked.

3) At the statistical analysis level: all data management and statistical analysis programs developed and used in the analysis will be documented. All versions generated will be dated, kept with accompanying documentation and archived. The original database will be stored. A derived database will be created for the new versions of the data in order to include recoding and computing of new variables, especially stratification of continuous variables, combination of modalities for categorical variables, calculation of composite indicators, etc.
4) At the results level, a data review will be done to ensure data integrity. A statistical analysis report including all the results will be provided for review and discussion. The final statistical report will take into account the reviewers' comments.
5) At the study level, all aspects of the study will be conducted according the standard operating procedures (SOPs) of IMS Real World Evidence Solutions and Medical Radar divisions. The study documents have been approved by people competent in medical and safety areas of IMS. According to IMS SOPs an independent review of the study results and report will be conducted by a person who was not in charge of their preparation.

9.8.3 Safeguards, security and traceability of calls

The operators of the call centre specialized in health surveys, will be assigned to the project and trained on the survey methodology prior to fieldwork. The phone calls will be traced using the call management software. All survey aspects from protocol development to the reporting of the results will

be conducted according to the SOPs of IMS Real World Evidence Solutions and Medical Radar divisions. These SOPs can be consulted on site (11).

9.9 LIMITATIONS OF THE RESEARCH METHODS

9.9.1 Possible selection bias due to voluntary participation

The selection bias of physicians participating in a survey is an inherent bias to any study based on volunteer participation. In order to quantify any selection bias, the distribution of each stratification criterion of healthcare professional (country and specialty) will be compared between participants and non-participants.

9.9.2 Limits inherent to web-surveys

The questionnaire includes general questions followed by specific ones. As the physicians may understand the right answer in subsequent questions, it would not be possible to go back in the questionnaire and edit answers in former questions.

In such surveys, the generalisation and external validity of the results is restricted to physicians who have an active email address and willing (and able) to answer a questionnaire online. These physicians may not be fully representative of the whole targeted population (12).

Among non-response bias, targeted physicians may also have activated filters in their mail box in order to block spams and unsolicited emails. They may not even see the invitation to participate in the survey if a very strict degree of message filtering is set. Having multiple email addresses could also be a critical situation. If the one used is not the primary address, or if the physicians do not check their email box frequently, they will not receive the invitation during the recruitment period. This is one of the reasons why the physicians will also be contacted by phone.

Moreover, web-surveys may promote social desirability bias which refers to the tendency of physicians to give socially desirable/expected responses instead of choosing those reflecting their current knowledge or behavior, e.g. physicians can copy-paste information collected online instead of giving their own opinions (12).

Social desirability can affect the validity of survey research findings, but the use of pre-populated items in the questionnaire could/tends to reduce this bias (13).

The access to the web-questionnaire interface will be strictly limited to the invited participants, with the possibility to participate only once and a traceability system. Thus stakeholder bias (multiple answers of people who have a personal interest in survey results and/or who incite peers to fulfill the survey in order to influence the results) or unverified respondents (when it is not possible to verify who responds) are not applicable.

9.9.3 Generalization of the survey results to the overall target population with adjustment

As the study design presents an over-sampling in some countries or specialties, and an under-sampling in others, survey results will not be generalized to the overall target population, except if a sample adjustment is applied. For more transparency and accuracy, both unweighted (i.e. raw data) and weighted results will be presented in the report. Since the IMS list may identify a limited number of physicians who were not targeted with the DHPC and the updated SmPC, the results may be impacted.

9.10 OTHER ASPECTS

None

10. PROTECTION OF HUMAN SUBJECTS

The survey is non-interventional and totally anonymous to the study sponsor. Data collected will remain absolutely confidential, and only aggregated data will be analysed and communicated in a report.

10.1 REGULATORY AND ETHICS CONSIDERATIONS

10.1.1 Ethical principles, laws and regulations

The survey will follow the regulatory and ethical requirements of each country. IMS will follow the European Pharmaceutical Marketing Research Association (EphMRA) guidelines (14) for all participating countries and specific local requirements will be applied.

10.2 PHYSICIANS INFORMATION

Physicians participating in the survey will be informed about targets of the investigation, the nature of the transmitted data, the intended use of data, recipients of these data, and their right of access and rectification to their personal data, as well as their right of objection to use their data or to IMS keeping their data.

10.2.1 Physicians compensations

Physicians will be offered a compensation for the time spent participating in this survey (which they may refuse).The time to complete the survey is estimated to be between 10 to 15 minutes, plus an additional 5 minutes for each prescription questionnaire..

The amount of this compensation will be determined according to the EphMRA recommendations and the Association of Opinion and Behaviour in health field research companies (ASOCS) charter, and which states:

“When it is necessary to compensate a physician in return to the time spent during an interview or a group meeting, the compensation must not exceed the fees commonly taken by the physician for his/her advice or consultation and must be proportional to the time provided. The compensations should be clearly stated prior to the physician's participation in the survey. They must be declared to the tax authorities in accordance with applicable laws”.

10.3 CONFIDENTIALITY

10.3.1 Patient confidentiality

The survey is non-interventional and totally anonymous to the study sponsor. Data collected will remain absolutely confidential, and only aggregated data will be communicated and analyzed.

10.3.2 Data confidentiality / Data security

The answers provided by the physicians will be collected in an anonymous way, only aggregated data and presented as a synthesis will be transmitted to the MAHs.

Participating physicians will access the website (https secured site) using a personalised login and their password.

Data will be recorded in a central database and tracked using an audit trail. The system will enable retrieving all introduced data at any time, and will include security elements to prevent others than authorized staff from accessing data. Each user will have a specific profile which will limit his/her use of the database. A security copy of the database and the application files will be made outside the server housing the web-based study. Security copies will be periodically made and stored outside this server. A copy of the data stored in the database will be transferred to MAHs at the end of the study.

Description of all elements of security and traceability will be available upon request.

10.4 RECORD RETENTION

The study documentation will be stored in the study master file.
The web questionnaires data will be stored on the survey database for 5 years.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 ADVERSE EVENT COLLECTION

Trained operators will record via the specific web-survey database all adverse events (AEs / adverse reactions (ARs) they become aware of that occurred in temporal association with MAHs' drug(s) under evaluation as defined in this protocol. Follow-up will be done by IMS if requested by Lupin.

The IMS Medical Radar AE electronic system will be used to record all identified AE in this project. The project name TMZ-DUS with the study Code: LUP/TMZ/2014/001a will be used in all AE reports and reconciliation form. All AE reports will be sent to: drugsafetyeurope@lupin.com.

AEs will be collected on an AE-collection form and forwarded by email (or fax) to Lupin within 24 hours after awareness. Additionally, the operators or other study personnel will record via IMS Medical Radar AE collection form the information related to the drug under evaluation as defined in this protocol, regardless of whether there is an associated serious or non-serious AE:

1) Instruct investigators/study personnel to collect all AEs they become aware of and are in temporal association the drug under evaluation in the survey protocol. Every effort should be made by the investigators/study personnel to obtain detailed information regarding the product name/ respective the MAH.
2) Instruct investigators/study personnel to forward the following information for the drug under evaluation in the study protocol to Lupin if the investigator/study personnel become aware of it, regardless of whether an associated serious adverse event (SAE)/ serious adverse reaction (SAR) or non-serious adverse event/reaction exists:
    - pregnancy exposures
    - suspected transmission of infectious agent
    - breast-feeding exposures
    - overdoses
    - misuse
    - abuse
    - off-label use
    - medication error
    - lack of drug effect

The MAHs collect product complaints on investigational products and drug delivery systems used in medical research studies in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements. Study personnel are instructed to report product complaints as they would for products in the marketplace in accordance with local regulations.

12. PLANS FOR DISSEMINATING AND COMMUNICATING SURVEY RESULTS

The survey will be registered in EU-PAS register (currently the ENCePP e-register of studies) by Lupin.

The statistical results will be discussed with and approved by MAH.

A survey report including the results of the twelve countries will be written in English, using the IMS Health template (which is based on the template included in the GVP module VIII) and following STROBE recommendations in MS Word format (9).

The final survey report validated by Lupin will be communicated to EMA.

13. REFERENCES

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14. EphMRA. Code of conduct 2013 [Internet]. 2013. Available from: http://www.ephmra.org/user_uploads/code%20of%20conduct%20oct%202013.pdf

14. ANNEXES

Annex 1

List of stand-alone documents

Number	Document reference number	Date	Title
1-Protocol	Version 2.0	18 July 2014	Evaluation of the Effectiveness of Risk Minimisation Measures: A Joint PASS Survey among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of Trimetazidine in Bulgaria, Czech Republic, Estonia, France, Hungary, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, and Spain
2-Questionnaire	Version 2.0	18 July 2014	Evaluation of the Effectiveness of Risk Minimisation Measures: A Joint PASS Survey among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of Trimetazidine in Bulgaria, Czech Republic, Estonia, France, Hungary, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, and Spain
3-DHPC	Version 1	September 2012	Direct Healthcare Professional Communication on restriction of indications for Trimetazidine containing products
4-Updated SmPC		September 2012	Summary of product characteristics Lupamadazine 35mg prolonged-release tablets

Annex 2

ENCePP checklist for study protocol

Study title: ***Evaluation of the Effectiveness of Risk Minimisation Measures: A Joint PASS Survey among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of Trimetazidine in Bulgaria, Czech Republic, Estonia, France, Hungary, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, and Spain***

Study reference number: tbd

Section 1: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the formulation of the research question clearly explain:				
1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	x	☐	☐	11,15
1.1.2 The objectives of the study?	x	☐	☐	11, 12, 16
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	x	☐	☐	12, 16, 18
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	x	
1.2.3 If applicable, that there is no *a priori* hypothesis?	☐	☐	x	

Comments:

For 2.1.3, see section 9.2 setting (p. 16, 17), section 9.5.1 Sampling plan (p.14, 15) of the protocol

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Is the source population described?	x	☐	☐	12, 18
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	x	☐	☐	14
2.2.2 Age and sex?	☐	☐	x	
2.2.3 Country of origin?	x	☐	☐	15, 16
2.2.4 Disease/indication?	☐	☐	x	
2.2.5 Co-morbidity?	☐	☐	x	

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.2.6 Seasonality?	☐	☐	x	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	x	☐	☐	12, 16-18

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☐	x	
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	x	☐	☐	12, 16
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	x	
3.4 Is sample size considered?	x	☐	☐	13, 18-21
3.5 Is statistical power calculated?	☐	☐	x	18-21

Comments:

The analysis will be done using descriptive statistics, but no specific endpoints are defined.

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	x	☐	☐	12, 13, 18
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self report, patient interview including scales and questionnaires, vital statistics, etc)	☐	☐	x	
4.1.3 Covariates?	☐	☐	x	
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose,				

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
number of days of supply prescription, daily dosage, prescriber)	x	☐	☐	17, 18 Questionnaire
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	x	
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	x	
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	x	
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☐	☐	x	
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	x	
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	x	

Comments:

For 8.2, please see survey questionnaire (stand alone document 2)

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☐	x	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	x	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	x	
5.4 Is exposure classified based on biological mechanism of action?	☐	☐	x	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	x	

Comments:

The survey aims to assess physicians'knowledge and prescribing conditions of Trimetazidine.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☐	x	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	x	

Comments:

The survey is descriptive. No specific endpoints are defined.

Section 7: Biases and Effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address:				
7.1.1 Selection biases?	x	☐	☐	27
7.1.2 Information biases?	x	☐	☐	27
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)				
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	x	
7.3 Does the protocol address known effect modifiers?	☐	☐	x	
(e.g. collection of data on known effect modifiers, anticipated direction of effect)				
7.4 Does the protocol address other limitations?	x	☐	☐	27

Comments:

For limitations inherent to web surveys please see p. 27 of the protocol.

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☐	☐	x	
8.2 Is the choice of statistical techniques described?	x	☐	☐	23-25
8.3 Are descriptive analyses included?	x	☐	☐	24
8.4 Are stratified analyses included?	x	☐	☐	18
8.5 Does the plan describe the methods for identifying:				

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.5.1 Confounders?	☐	☐	x	
8.5.2 Effect modifiers?	☐	☐	x	
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☐	☐	x	
8.6.2 Effect modification?	☐	☐	x	

Comments:

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	x	☐	☐	28
9.2 Are methods of quality assurance described?	x	☐	☐	26
9.3 Does the protocol describe quality issues related to the data source(s)?	x	☐	☐	27
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	x	☐	☐	18-19
9.5 Does the protocol specify timelines for				
9.5.1 Study start?	x	☐	☐	13
9.5.2 Study progress? (e.g. end of data collection, other milestones)	x	☐	☐	13
9.5.3 Study completion?	x	☐	☐	13
9.5.4 Reporting? (i.e. interim reports, final study report)	x	☐	☐	13
9.6 Does the protocol include a section to document future amendments and deviations?	x	☐	☐	14
9.7 Are communication methods to disseminate results described?	x	☐	☐	29-30
9.8 Is there a system in place for independent review of study results?	x	☐	☐	26

Comments:

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☐	☐	x	
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	x	
10.3 Have data protection requirements been described?	x	☐	☐	28

Comments:

Please see section 12 of the protocol (p.29-30).

Name of principle investigator: _____

Date: 20 Nov 2014

Signature:

Annex 3

Additional information

List of Companies - MAHs for generic Trimetazidine containing products that are part of the consortium.

These companies also represent their Affiliates and/or other Companies belonging to the same group and/or licensees holding Marketing Authorizations in various Member States as mentioned in Annex-3.

1. Actavis Group PTC ehf.
2. Alvogen IPCo S.a.r.l.
3. Chemical Works of Gedeon Richter Plc.
4. Generis Farmacêutica, S.A.
5. Lek Pharmaceuticals d.d. (Sandoz Group)
6. Labesfal Genéricos S.A.
7. Laboratorios Cinfa, S.A.
8. Lupin (Europe) Limited
9. Mylan S.A.S.
10. Teva Pharmaceuticals Europe B.V.

List of Trimetazidine containing products marketed in various Member States by companies who are part of the consortium

Member State EU/EEA	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Route of administration
Estonia	Actavis Group PTC ehf., Reykjavikurvegi 76-78 220 Hafnarfjordur Iceland	Trimetazidine Actavis	35mg	Modified-release tablets	Oral use
Bulgaria	Actavis Group PTC ehf., Reykjavikurvegi 76-78 220 Hafnarfjordur Iceland	Vascotasin	35mg	Modified-release tablets	Oral use
Czech Republic	Actavis Group PTC ehf., Reykjavikurvegi 76-78 220 Hafnarfjordur Iceland	Trimetazidin Actavis 35mg	35mg	Modified-release tablets	Oral use
Hungary	Actavis Group PTC ehf., Hafnarfjordur Reykjavikurvegi 76-78 220 Hafnarfjordur Iceland	Vascotasin 35 mg módosított hatóanyag-leadású tabletta	35mg	Modified-release tablets	Oral use
Lithuania	Actavis Group PTC ehf., Reykjavikurvegi 76-78 220 Hafnarfjordur Iceland	Trimetazidine Actavis 35 mg modifikuoto atpalaidavimo tabletės	35mg	Modified-release tablets	Oral use
Latvia	Actavis Group PTC ehf., Reykjavikurvegi 76-78, 220 Hafnarfjordur Iceland	Trimetazidine Actavis	35mg	Modified-release tablets	Oral use
Poland	Actavis Group PTC ehf., Reykjavikurvegi 76-78 220 Hafnarfjordur Iceland	Vascotazin	35mg	Modified-release tablets	Oral use

Slovak Republic	Actavis Group PTC ehf., Reykjavikurvegi 76- 78 220 Hafnarfjordur Iceland	Vascotazin 35 mg	35mg	Modified-release tablets	Oral use

Member State EU/EEA	**Marketing authorisation holder**	**Product name**	**Strength**	**Pharmaceutical form**	**Route of admini stratio n**
Bulgaria	Alvogen IPCo S.a.r.l. Luxembourg	Trimetacor 35 mg tablets	35 mg	Prolonged Release Tablets	Oral use
Hungary	Aramis Pharma Kft.	Mezitan 35 mg módosított hatóanyag-leadású tabl	35 mg	Prolonged Release Tablets	Oral use
Romania	LABORMED PHARMA S.A. Bd. Theodor Pallady nr. 44B sector 3, Bucureşti România	Trimetazidina LPH 20 mg comprimate filmate	20 mg	Film-coated tablet	Oral use
Romania	LABORMED PHARMA S.A. Bd. Theodor Pallady nr. 44B sector 3, Bucureşti România	Trimetazidina LPH 35mg comprimate cu eliberare modificata	35 mg	Modified-release tablets	Oral use

Member State EU/EEA	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Route of administration
Bulgaria	Gedeon Richter Plc. Gyömrői út 19-21 H- 1103 Budapest Hungary	Moduxin MR	35 mg	Prolonged-release film-coated tablets	Oral use
Czech Republic	Gedeon Richter Plc. Gyömrői út 19-21 H- 1103 Budapest Hungary	Protevasc	35 mg	Prolonged-release film-coated tablets	Oral use
Hungary	Gedeon Richter Plc. Gyömrői út 19-21 H- 1103 Budapest Hungary	Moduxin MR	35 mg	Prolonged-release film-coated tablets	Oral use
Latvia	Gedeon Richter Plc. H-1103 Budapest Gyömrői út 19-21 Hungary	Moduxin 35 mg ilgstošās darbības tabletes	35 mg	Prolonged-release film-coated tablets	Oral use
Lithuania	Gedeon Richter Plc. Gyömrői út 19-21 H- 1103 Budapest Hungary	Moduxin	35 mg	Prolonged-release film-coated tablets	Oral use
Poland	Gedeon Richter Polska Sp. z o.o. ul. ks. J. Poniatowskiego 5 05-825 Grodzisk Mazowiecki Poland	Protevasc SR	35 mg	Prolonged-release film-coated tablets	Oral use
Romania	Gedeon Richter Romania S.A. Str. Cuza - Vodă nr. 99 –105 Târgu – Mureş Romania	MODUXIN MR 35 mg, comprimate cu eliberare prelungită	35 mg	Prolonged-release film-coated tablets	Oral use
Romania	Gedeon Richter Romania S.A. Str. Cuza - Vodă nr. 99 –105 Târgu – Mureş Romania	MODUXIN 20 mg, comprimate filmate	20 mg	Film-coated tablets	Oral Use
Slovak Republic	Gedeon Richter Plc. Gyömrői út 19-21 H- 1103 Budapest Hungary	Protevasc	35 mg	Prolonged-release film-coated tablets	Oral use

Member State EU/EEA	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Route of administration
Portugal	Generis Farmacêutica, S.A.	Trimetazidina Generis	35 mg	Prolonged release tablets	Oral use
Portugal	Generis Farmacêutica, S.A.	Trimetazidina Generis 20 mg Comprimidos Revestidos	20 mg	Coated tablets	Oral use

Member State EU/EEA	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Route of administration
Bulgaria	Sandoz Pharmaceuticals d.d Verovškova 57, 1526 Ljubljana Slovenia	Energotrim 35 mg prolonged release tablet	35 MG	PROLONGED RELEASE TABLET	Oral use
Latvia	Sandoz Pharmaceuticals d.d Verovškova 57, 1526 Ljubljana Slovenia	Zidmetin 35 mg ilgstošās darbības tabletes	35 MG	PROLONGED RELEASE TABLET	Oral use
Estonia	Sandoz Pharmaceuticals d.d. Verovškova 57 1526 Ljubljana Slovenia	Zidmetin	35 MG	PROLONGED RELEASE TABLET	Oral use
Hungary	Sandoz Hungária Kft. Bartók Béla út 43-47. 1114 Budapest Hungary	Trimetazidine Sandoz 35 mg retard tabletta	35 MG	PROLONGED RELEASE TABLET	Oral use
Lithuania	Sandoz Pharmaceuticals d.d Verovškova 57, 1526 Ljubljana Slovenia	Zidmetin 35mg pailginto atpalaidavimo tabletės	35 MG	PROLONGED RELEASE TABLET	Oral use
Romania	S.C. SANDOZ S.R.L. Str. Livezeni 7A 540472 Targu Mures Romania	Trimeluzine 35 mg comprimate cu eliberare prelungită	35 MG	PROLONGED RELEASE TABLET	Oral use
Portugal	Sandoz Farmacêutica, Lda. Alameda da Beloura, Edifício 1, 2º - Escritório 15 2710-693 Sintra Portugal	Trimetazidina ltraxel	35 MG	PROLONGED RELEASE TABLET	Oral use
Poland	Sandoz GmbH Biochemiestrasse 10 6250 Kundl Austria	Dimesar	35 MG	PROLONGED RELEASE TABLET	Oral use

Member State EU/EEA	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Route of administration
Slovenia	LEK PHARMACEUTICALS D.D. LJUBLJANA Verovškova 57, 1526 Ljubljana Slovenia	Trimeluzine 35 mg tablete s podaljšanim sproščanjem	35 MG	PROLONGED RELEASE TABLET	Oral use
Croatia	SANDOZ D.O.O. Maksimirska 120 1000 Zagreb Croatia	Vazidin 35 mg tablete s produljenim oslobađanjem	35 MG	PROLONGED RELEASE TABLET	Oral use
Portugal	Sandoz Farmacêutica, Lda. Alameda da Beloura, Edifício 1, 2º - Escritório 15 2710-693 Sintra Portugal	Trimetazidina Sandoz	35 MG	PROLONGED RELEASE TABLET	Oral use

Member State EU/EEA	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Route of administration
Portugal	Labesfal Genéricos, S.A.	Trimetazidina Labesfal 20 mg comprimidos revestidos	20 mg	Coated tablet	Oral use
Portugal	Labesfal Genéricos, S.A.	Trimetazidina Labesfal	35 mg	Prolonged-release tablet	Oral use

Member State EU/EEA	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Route of administration
Spain	Laboratorios Cinfa, S.A. Olaz-Chipi, 10 (Pol. Areta)31620 Huarte (Spain)	TRIMETAZIDINA CINFA 20 mg comprimidos recubiertos con película EFG	20 MG	FILM-COATED TABLETS	Oral use
Portugal	Cinfa Portugal, Lda. Avda. Tomás Ribeiro, 43; Bloco 1-4B (Edif. Neopark) 2790-221 Carnaxide (Portugal)	Trimetazidina Cinfa 20 mg Comprimidos revestidos por película	20 MG	FILM-COATED TABLETS	Oral use

Member State EU/EEA	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Route of administration
Germany	Lupin (Europe) Ltd Victoria Court, Bexton Road, Knutsford, Cheshire UK	Lupamadazine 35mg Retardtabletten	35mg	Prolonged release tablets	Oral use
Portugal	PharmaKERN Portugal, Lda. Ed. Atlas II, Av. José Gomes Ferreira, N.º 11, 3º, SL 31. Miraflores 1495-139 Algés Portugal	Trimetazidina Pharmakern 35mg Comprimido de libertação prolongada	35mg	Prolonged release tablets	Oral use
Lithuania	SIA Ingen Pharma, Latvia	Trimetazidine Ingen Pharma	35mg	Prolonged release tablets	Oral use

Member State EU/EEA	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Route of administration
Bulgaria	Mylan S.A.S. 117 Allee des Parcs 69800 Saint Priest France	TRIMETAZIGEN MR 35 mg prolonged - release tablets	35 mg	Modified release tablet	Oral use
Czech Republic	Mylan S.A.S 117 Alleé des Parcs 69 800, Saint-Priest France	Trimetazidin Mylan 35 mg, tablety s prodlouženým uvolňováním	35 mg	Modified release tablet	Oral use
Germany	Mylan S.A.S 117 Alleé des Parcs 69 800, Saint-Priest France	Lutrazine 35 mg Retardtabletten	35 mg	Modified release tablet	Oral use
Hungary	Mylan S.A.S 117 Allee des Parcs 69800 Saint Priest France	Trimetazidine Mylan 35 mg retard tabletta	35 mg	Modified release tablet	Oral use
Poland	Mylan S.A.S 117 Alleé des Parcs 69 800, Saint-Priest France	Trioxigen	35 mg	Modified release tablet	Oral use
Portugal	Mylan, Lda. Parque Expo - Edifício Atlantis Avenida D. João II, Lote 1.06.2.2 C - 7.3 e 7.4 1990-095 Lisboa	Trimetazidina Mylan	35 mg	Modified release tablet	Oral use
Romania	MYLAN S.A.S. 117, Allée des Parcs 69800 Saint Priest France	TRIMETAZIDINA MYLAN 35 mg, comprimate cu eliberare prelungita	35 mg	Modified release tablet	Oral use
Slovakia	Mylan S.A.S 117, Allée des Parcs 69800 Saint Priest France	Trimetazidin Mylan 35 mg	35 mg	Modified release tablet	Oral use

Member State EU/EEA	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Route of administration
France	MYLAN S.A.S 117, allée des Parcs 69800 Saint-Priest France	TRIMETAZIDINE MYLAN 20 mg, comprimé pelliculé	20 mg	Tablet	Oral use
France	MYLAN S.A.S 117, allée des Parcs 69800 Saint-Priest France	TRIMETAZIDINE MYLAN 20 mg/ml, solution buvable en gouttes	20 mg/mL	Oral solution	Oral use
France	MYLAN S.A.S 117, allée des Parcs 69800 Saint-Priest France	TRIMETAZIDINE MYLAN 35 mg, comprimé pelliculé à libération modifiée	35 mg	Modified release tablet	Oral use
Portugal	Mylan, Lda. Parque Expo - Edifício Atlantis Avenida D. João II, Lote 1.06.2.2 C - 7.3 e 7.4 1990-095 Lisboa Portugal	Trimetazidina Mylan	20 mg	Tablet	Oral use

Member State EU/EEA	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Route of administration
Bulgaria	ratiopharm GmbH; Ulm, Germany	Trimetazidine-ratiopharm 35 mg	35 mg	modified release tablet	oral use
Bulgaria	ratiopharm GmbH; Ulm, Germany	Trimetazidine-ratiopharm 35 mg	35 mg	modified release tablet	oral use
Bulgaria	ratiopharm GmbH; Ulm, Germany	Trimetazidine-ratiopharm 35 mg	35 mg	modified release tablet	oral use
Bulgaria	Teva Pharmaceuticals Bulgaria EOOD, 15 N. V Gogol Str., 1124 Sofia, Bulgaria	TevaTrim 35 mg prolonged-release tablets	35 mg	modified release tablet	oral use
Bulgaria	Teva Pharmaceuticals Bulgaria EOOD, 15 N. V Gogol Str., 1124 Sofia, Bulgaria	TevaTrim 35 mg prolonged-release tablets	35 mg	modified release tablet	oral use
Bulgaria	Teva Pharmaceuticals Bulgaria EOOD, 15 N. V Gogol Str., 1124 Sofia, Bulgaria	TevaTrim 35 mg prolonged-release tablets	35 mg	modified release tablet	oral use
Bulgaria	Teva Pharmaceuticals Bulgaria EOOD, 15 N. V Gogol Str., 1124 Sofia, Bulgaria	TevaTrim 35 mg prolonged-release tablets	35 mg	modified release tablet	oral use

Member State EU/EEA	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Route of administration
Bulgaria	Teva Pharmaceuticals Bulgaria EOOD, 15 N. V Gogol Str., 1124 Sofia, Bulgaria	TevaTrim 35 mg prolonged-release tablets	35 mg	modified release tablet	oral use
Bulgaria	Teva Pharmaceuticals Bulgaria EOOD, 15 N. V Gogol Str., 1124 Sofia, Bulgaria	TevaTrim 35 mg prolonged-release tablets	35 mg	modified release tablet	oral use
Czech Republic	Teva Pharmaceuticals CR, s.r.o.; Prague, Czech Republic	Trimetazidin Teva retard 35 mg	35 mg	modified release tablet	oral use
Czech Republic	Teva Pharmaceuticals CR, s.r.o.; Prague, Czech Republic	Trimetazidin Teva retard 35 mg	35 mg	modified release tablet	oral use
Czech Republic	Teva Pharmaceuticals CR, s.r.o.; Prague, Czech Republic	Trimetazidin Teva retard 35 mg	35 mg	modified release tablet	oral use
Estonia	Teva Pharma B.V.; Computerweg 10, 3542 DR Ultrecht The Netherlands	Trimetazidine Teva 35mg	35 mg	modified release tablet	oral use
France	ratiopharm GmbH; Ulm, Germany	Trimetazidine ratiopharm 20 mg/ml, solution buvable en gouttes	20 mg / ml	oral solution	oral use
France	ratiopharm GmbH; Ulm, Germany	Trimetazidine ratiopharm 20 mg, comprimé enrobé	20 mg	tablet	oral use

Member State EU/EEA	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Route of administration
France	ratiopharm GmbH; Ulm, Germany	Trimetazidine ratiopharm 20 mg, comprimé enrobé	20 mg	tablet	oral use
France	ratiopharm GmbH; Ulm, Germany	Trimetazidine ratiopharm 20 mg, comprimé enrobé	20 mg	tablet	oral use
France	Teva Santé, Le Palatin 1 1 cours du Triangle 9296 Paris la Défense Cedex France	Trimetazidine Teva 20 mg/ml. solution buvable en gouttes	20 mg / ml	oral solution	oral use
France	Teva Santé, Le Palatin 1 1 cours du Triangle 9296 Paris la Défense Cedex France	Trimetazidine Teva 20 mg. comprime pellicule	20 mg	tablet	oral use
France	Teva Santé, Le Palatin 1 1 cours du Triangle 9296 Paris la Défense Cedex France	Trimetazidine Teva 20 mg. comprime pellicule	20 mg	tablet	oral use
France	Teva Santé, Le Palatin 1 1 cours du Triangle 9296 Paris la Défense Cedex France	Trimetazidine Teva 20 mg. comprime pellicule	20 mg	tablet	oral use
France	Teva Santé, Le Palatin 1 1 cours du Triangle 9296 Paris la Défense Cedex France	Trimetazidine Teva 20 mg. comprime pellicule	20 mg	tablet	oral use

Member State EU/EEA	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Route of administration
Hungary	ratiopharm GmbH; Ulm, Germany	Trimetazidin-ratiopharm 35 mg retard tabletta	35 mg	modified release tablet	oral use
Latvia	Teva Pharma B.V.; Computerweg 10, 3542 DR Ultrecht The Netherlands	Trimetazidine Teva 35mg ilgstosas darbibas tabletes	35 mg	modified release tablet	oral use
Latvia	Teva Pharma B.V.; Computerweg 10, 3542 DR Ultrecht The Netherlands	Trimetazidine Teva 35mg ilgstosas darbibas tabletes	35 mg	modified release tablet	oral use
Latvia	Teva Pharma B.V.; Computerweg 10, 3542 DR Ultrecht The Netherlands	Trimetazidine Teva 35mg ilgstosas darbibas tabletes	35 mg	modified release tablet	oral use
Lithuania	Teva Pharma B.V.; Computerweg 10, 3542 DR Ultrecht The Netherlands	Trimetazidine Teva 35 mg pailginto atpalaidavimo tabletés	35 mg	modified release tablet	oral use
Lithuania	Teva Pharma B.V.; Computerweg 10, 3542 DR Ultrecht The Netherlands	Trimetazidine Teva 35 mg pailginto atpalaidavimo tabletés	35 mg	modified release tablet	oral use
Lithuania	Teva Pharma B.V.; Computerweg 10, 3542 DR Ultrecht The Netherlands	Trimetazidine Teva 35 mg pailginto atpalaidavimo tabletés	35 mg	modified release tablet	oral use
Poland	ratiopharm GmbH; Ulm, Germany	Trimetaratio	20 mg	tablet	oral use
Member State EU/EEA	**Marketing authorisation holder**	**Product name**	**Strength**	**Pharmaceutical form**	**Route of administration**

Poland	ratiopharm GmbH; Ulm, Germany	Trimetazidine-ratiopharm PR	35 mg	modified release tablet	oral use
Poland	ratiopharm GmbH; Ulm, Germany	Trimetazidine-ratiopharm PR	35 mg	modified release tablet	oral use
Portugal	MEPHA – INVESTIGAÇÃO; Lagoas Park, Edificio 5-A, Piso 2 2740-298, Porto Salvo, Portugal	Trimetazidina Mepha 20 mg Comprimidos Revestidos	20 mg	tablet	oral use
Portugal	MEPHA – INVESTIGAÇÃO; Lagoas Park, Edificio 5-A, Piso 2 2740-298, Porto Salvo, Portugal	Trimetazidina Mepha 20 mg Comprimidos Revestidos	20 mg	tablet	oral use
Portugal	MEPHA – INVESTIGAÇÃO; Lagoas Park, Edificio 5-A, Piso 2 2740-298, Porto Salvo, Portugal	Trimetazidina Mepha LP 35 mg Comprimidos de Libertação Prolongada	35 mg	modified release tablet	oral use
Portugal	MEPHA – INVESTIGAÇÃO; Lagoas Park, Edificio 5-A, Piso 2 2740-298, Porto Salvo, Portugal	Trimetazidina Mepha LP 35 mg Comprimidos de Libertação Prolongada	35 mg	modified release tablet	oral use
Portugal	Ratiopharm - Comercio e Industria de Produtos Farmaceuticos, Lda.; Edificio 5 A, Piso 2, Porto Salvo, Portugal	Trimetazidina ratiopharm	20 mg	tablet	oral use

Member State EU/EEA	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Route of administration
Portugal	Ratiopharm - Comercio e Industria de Produtos Farmaceuticos, Lda.; Edificio 5 A, Piso 2, Porto Salvo, Portugal	Trimetazidina ratiopharm	20 mg	tablet	oral use
Portugal	Ratiopharm - Comercio e Industria de Produtos Farmaceuticos, Lda.; Edificio 5 A, Piso 2, Porto Salvo, Portugal	Trimetazidina Clijier	35 mg	modified release tablet	oral use
Portugal	Ratiopharm - Comercio e Industria de Produtos Farmaceuticos, Lda.; Edificio 5 A, Piso 2, Porto Salvo, Portugal	Trimetazidina Clijier	35 mg	modified release tablet	oral use
Portugal	Ratiopharm - Comercio e Industria de Produtos Farmaceuticos, Lda.; Edificio 5 A, Piso 2, Porto Salvo, Portugal	Trimetazidina Ratiopharm, 35mg, comprimidos de libertação prolongada.	35 mg	modified release tablet	oral use

Member State EU/EEA	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Route of administration
Portugal	Ratiopharm - Comercio e Industria de Produtos Farmaceuticos, Lda.; Edificio 5 A, Piso 2, Porto Salvo, Portugal	Trimetazidina Ratiopharm, 35mg, comprimidos de libertação prolongada.	35 mg	modified release tablet	oral use
Portugal	Ratiopharm - Comercio e Industria de Produtos Farmaceuticos, Lda.; Edificio 5 A, Piso 2, Porto Salvo, Portugal	Trimetazidina Clijier	35 mg	modified release tablet	oral use
Portugal	Teva Pharma - Produtos Farmacêuticos Lda; Lisbon, Portugal	Trimetazidina Teva 20 mg Comprimidos revestidos	20 mg	tablet	oral use
Portugal	Teva Pharma - Produtos Farmacêuticos Lda; Lisbon, Portugal	Trimetazidina Teva 20 mg Comprimidos revestidos	20 mg	tablet	oral use
Portugal	Teva Pharma - Produtos Farmacêuticos Lda; Lisbon, Portugal	Trimetazidina Teva 35 mg comprimidos de libertação prolongada	35 mg	modified release tablet	oral use
Portugal	Teva Pharma - Produtos Farmacêuticos Lda; Lisbon, Portugal	Trimetazidina Teva 35 mg comprimidos de libertação prolongada	35 mg	modified release tablet	oral use
Member State EU/EEA	**Marketing authorisation holder**	**Product name**	**Strength**	**Pharmaceutical form**	**Route of administration**

Slovakia	ratiopharm GmbH; Ulm, Germany	Trimetazidin-ratiopharm 20 mg	20 mg	tablet	oral use
Slovakia	ratiopharm GmbH; Ulm, Germany	Trimetazidin-ratiopharm 20 mg	20 mg	tablet	oral use
Slovakia	ratiopharm GmbH; Ulm, Germany	Trimetazidin-ratiopharm 20 mg	20 mg	tablet	oral use
Slovakia	ratiopharm GmbH; Ulm, Germany	Trimetazidin-ratiopharm 20 mg	20 mg	tablet	oral use
Slovakia	ratiopharm GmbH; Ulm, Germany	Trimetazidin-ratiopharm 20 mg	20 mg	tablet	oral use
Slovakia	ratiopharm GmbH; Ulm, Germany	Trimetazidin ratiopharm retard 35 mg	35 mg	modified release tablet	oral use
Slovakia	ratiopharm GmbH; Ulm, Germany	Trimetazidin ratiopharm retard 35 mg	35 mg	modified release tablet	oral use
Slovakia	ratiopharm GmbH; Ulm, Germany	Trimetazidin ratiopharm retard 35 mg	35 mg	modified release tablet	oral use
Spain	Laboratorios Davur S.L;. C/ Teide, 4. Parque Empresarial La Marina., 28703 San Sebastian de los Reyes (MADRID) Spain	Trimetazidina Davur 20 mg comprimidos recubiertos EFG	20 mg	tablet	oral use

Member State EU/EEA	Marketing authorisation holder	Product name	Strength	Pharmaceutical form	Route of administration
Spain	Laboratorios Davur S.L;. C/ Teide, 4. Parque Empresarial La Marina., 28703 San Sebastian de los Reyes (MADRID) Spain	Trimetazidina Davur 35 mg comprimidos de liberacion prolongada	35 mg	modified release tablet	oral use
Spain	ratiopharm España, S.A.; C/Anabel Segura 11, Edifico Albatros B, 1a planta, Alcobendas, 28108 Madrid, Spain	Trimetazidina ratiopharm 20 mg comprimidos recubiertos con película EFG	20 mg	tablet	oral use
Spain	ratiopharm España, S.A.; C/Anabel Segura 11, Edifico Albatros B, 1a planta, Alcobendas, 28108 Madrid, Spain	Trimetazidina ratiopharm 20 mg comprimidos recubiertos con película EFG	20 mg	tablet	oral use
Spain	Teva Pharma, S.L.U.; Alcobendas, Madrid, Spain	Trimetazidina Belmac 35 mg comprimidos de liberación prolongada	35 mg	modified release tablet	oral use
Slovakia	Deml Group s.r.o., Jeneweinova 51a 617 00 Brno Czech Republic	Trimetazidin - DemlGroup PR 35 mg	35 mg	modified release tablet	oral use

Slovakia	Deml Group s.r.o., Jeneweinova 51a 617 00 Brno Czech Republic	Trimetazidin - DemlGroup PR 35 mg	35 mg	modified release tablet	oral use
Member State EU/EEA	**Marketing authorisation holder**	**Product name**	**Strength**	**Pharmaceutical form**	**Route of administration**
Slovakia	Deml Group s.r.o., Jeneweinova 51a	Trimetazidin - DemlGroup PR 35 mg	35 mg	modified release tablet	oral use

	617 00 Brno Czech Republic				
Slovakia	Deml Group s.r.o., Jeneweinova 51a 617 00 Brno Czech Republic	Trimetazidin - DemlGroup PR 35 mg	35 mg	modified release tablet	oral use
Slovakia	Deml Group s.r.o., Jeneweinova 51a 617 00 Brno Czech Republic	Trimetazidin - DemlGroup PR 35 mg	35 mg	modified release tablet	oral use
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Direct Healthcare Professional Communication

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27th September 2012

Direct Healthcare Professional Communication on restriction of indications for Trimetazidine containing products.

Dear healthcare professional,

Summary

- Trimetazidine-containing products should only be prescribed in adult patients as add-on therapy for the symptomatic treatment of stable angina pectoris inadequately controlled by first-line anti-anginal therapies or to patients intolerant to such therapy.
- The benefit/risk profile of Trimetazidine is no longer indicated in the symptomatic treatment of vertigo and tinnitus and the symptomatic treatment of the decline in visual acuity and visual field disturbances presumably of vascular origin. Patients currently on treatment should have their treatment reviewed at the next routine appointment.
- Trimetazidine should not be used in patients with Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders.
- Trimetazidine should not be used in patients with severe renal impairment. For patients with moderate renal impairment and the elderly the dose should be reduced.

Further information

Following a review of all available data, the CHMP (The European Medicines Agency´s committee for Medicinal Products for Human Use) concluded that the benefit/risk balance of Trimetazidine-containing products only remains positive in a limited population of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line anti-anginal therapies as add-on therapy. For all other indications, the efficacy has not been considered as sufficiently documented according to current guidelines and methodology. Thus, the Committee found that the risk outweighed the evidence for clinically important efficacy and concluded that all other indications should be withdrawn from the marketing authorisations of these medicines.

The safety review focused on the occurrence of parkinsonian symptoms which can be associated with the use of trimetazidine. Trimetazidine can cause or worsen parkinsonian symptoms (tremor, akinesia, hypertonia), which should be investigated, especially in elderly patients and patients with renal insufficiency in whom an increased exposure is expected.

Therefore, trimetazidine is contraindicated in patients with Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome and other movement and in patients with severe renal impairment.

The occurrence of movement disorders such as parkinsonian symptoms, restless leg syndrome, tremors, gait instability should lead to definitive withdrawal of trimetazidine. Cases which have been reported are usually reversible after treatment discontinuation. For the majority of the patients who recovered, the

symptoms disappeared within 4 months after trimetazidine withdrawal. If parkinsonian symptoms persist more than 4 months after drug discontinuation, a neurologist opinion should be sought. Overall, in doubtful cases, patients should be referred to a neurologist for appropriate investigations.

For further information, please refer to the attached Summary of the Product Characteristics.

Call for reporting

You are reminded to report any suspected adverse reactions in accordance with the national spontaneous reporting system *to www.imb.ie.*

Communication information

Should you have any questions or require additional information please contact Aoife McAuliffe, Medical and Regulatory Affairs Manager, Servier Laboratories Ireland, Tel: 01-6638110.

Yours sincerely,

Mr Yann Mazeman, PharmD

General Manager