`

Drug utilization study of Azilsartan medoxomil in Germany

Takeda Protocol Number: Azilsmedox-5007

PREPARED FOR

PAUL DOLIN, DIRECTOR EUROPEAN EPIDEMIOLOGY
TAKEDA GLOBAL RESEARCH & DEVELOPMENT CENTRE (EUROPE) LTD

IMS REF: 954939
VERSION: 2.0
DATE: FEBRUARY 13, 2014

PREPARED BY

Birgit Ehlken, Director
Mark Lamotte, Senior Principal

IMS Real-World Evidence Solutions and
Health Economics & Outcomes Research
Erika-Mann-Str. 5
80636 München, Germany

Table of Contents

Background and Rationale

Azilsartan medoxomil
Takeda has developed Edarbi (azilsartan medoxomil), an angiotensin II receptor antagonist (ARB), for the treatment of essential hypertension in adults on the basis of 8 main studies involving over 6,000 patients with essential hypertension. In two studies with azilsartan medoxomil taken alone compared with placebo, patients had an average decrease in systolic blood pressure of about 13.5 mmHg on azilsartan medoxomil 40 mg and a decrease of about 14.5 mmHg on azilsartan medoxomil 80 mg after 6 weeks. This compares with a decrease of 0.3 to 1.4 mmHg in the patients taking placebo. When azilsartan medoxomil alone was compared with other medicines, 80 mg of azilsartan medoxomil was more effective in lowering blood pressure than the highest approved dose of valsartan (320 mg) and olmesartan medoxomil (40 mg). Azilsartan medoxomil 40 and 80 mg was also more effective than ramipril (10 mg). The studies also showed that Azilsartan medoxomil, when taken in combination with other medicines, can produce additional decreases in blood pressure compared with when these medicines are taken without azilsartan medoxomil.

Azilsartan medoxomil is prescribed by primary care phycisians. Azilsartan medoxomil is available as tablets (20 mg, 40 mg and 80 mg). Azilsartan medoxomil must not be used in people who are hypersensitive to azilsartan medoxomil or any of the other ingredients. It must not be used in women who are more than three months pregnant. Its use during the first three months of pregnancy is also not recommended.

Current Summary of Product Characteristics (SPC) of azilsartan medoxomil is included in Appendix A.

Post-authorization drug utilization
On December 7th 2011, the European Commission granted marketing authorisation for Azilsartan medoxomil valid throughout the European Union. Takeda launched Azilsartan medoxomil in January 2012 in Germany.

Uncertainties are present regarding the dosing and safety of azilsartan medoxomil in complicated patients, such as the very elderly (> 75 years), patients with an activated renin angiotensin aldosterone system (e.g. patients with heart failure), and patients with renal and liver insufficiency.

During the approval process, Takeda as the Marketing Authorisation Holder (MAH) of azilsartan medoxomil committed to conduct a post-authorisation drug utilisation study investigating the prescribing and use of azilsartan medoxomil in the population and more specifically to clarify and estimate the degree of off-label use. Descriptive retrospective database analyses of patient demographics, morbidities and azilsartan medoxomil drug utilization are part of the pharmacovigilance plan.

Takeda request
Takeda has requested IMS to provide a proposal to implement a retrospective drug utilization study (DUS) for azilsartan medoxomil, using the IMS® Disease Analyzer (DA) general phycisian (GP) panel database. The following sections of this proposal specify the objectives of the project; outline the proposed approach; describe the recommended data source; and detail the tasks, budget, and timeline for the project.

Objective

The primary study objective is to describe the population being prescribed azilsartan medoxomil in terms of demographics (age and gender) and ICD-10 CM based (co-) morbidities.

Secondary objective will be to describe drug utilization of azilsartan medoxomil (as described in Section 5, Methodology, Study Endpoints).

The information of the DUS will be used to estimate the proportion of patients who have received azilsartan medoxomil according to the age and dosage profile in the SPC.

General Approach

IMS proposes to conduct retrospective analyses of longitudinal patient-centric electronic medical records (EMR) data collected continuously over time: IMS® DA.

The country of interest is Germany.

General steps in the project approach are listed below and will be described in more detail further on in this proposal:

- Face to face kick off meeting
- Support to Takeda in Takeda's communication with EMA
- Analysis plan development and table shells (including sample precision estimates)
- Data extraction and development of study data matrix (year 1 and year 5)
- Database analyses (year 1 and year 5)
- Reporting (year 1 and year 5):
    - Microsoft Excel spreadsheet report with results
    - Final summary report in Word

Report summary in PowerPoint

Data source

IMS suggests using longitudinal patient level data in Germany; i.e., the GP panel of IMS® DA. Currently, the most recent data available include December 2013.

The German IMS® DA database is based on a rolling patient records continuously collected from 1,600 computerized practices (including specialists) throughout Germany. There are 7 million patient records and more than 44 million prescriptions. The database includes GP but also specialist practices. Specialist practices include diabetologists, cardiologists, gynecologists, neurologists, orthopedics, pediatricians and urologists. It is not possible to track an individual between different panels; but IMS can analyze what the GP panel records about essential hypertension, and separately if needed the cardiologist panel records about essential hypertension. IMS samples practices with practice management software from Compugroup. The sample is designed to be representative of Germany.

Since azilsartan medoxomil in Germany is currently only prescribed by GPs, only the GP panel will be included in the current scope of work proposed. In the period January 2012-December 2013, the total number of unique patients with at least one prescription of azilsartan medoxomil

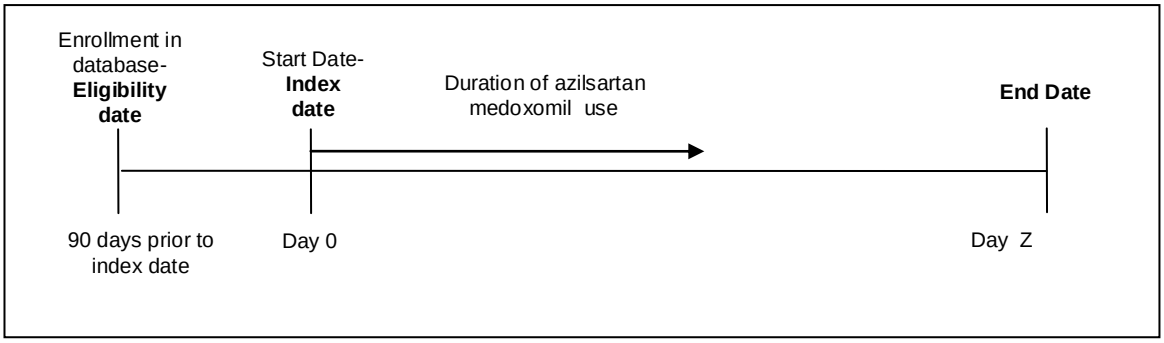
was n = 1156 patients, final sample size in study may vary based on start of study and in- and exclusion criteria applied (see Section 5, sample size). Should azilsartan medoxomil also become prescribed by specialists, additional panel data can be added at a later point in time for an additional data access and extraction fee (specialist data are not part of current scope of work proposed).

More information on validity of the database is published by Becher et al.[i] and, additional information is also provided in Section VII, Study Strengths and Limitations.

Methodology

Cohort selection:
All patients (of any age) with at least one prescription for azilsartan medoxomil (ATC code C09CA09) in the reporting period will be extracted in the database, using ATC codes and drug name for identification. Date at first observed prescription is defined as the index date. Patient data will be analyzed from index date to end of data collection, or end of study period whichever occurs first.

Patients will be included in the study cohort if they had a record in the database for at least 90 days before the index date in order to determine prior medication use and the presence of certain illnesses:



Additional patient inclusion / exclusion criteria will include:

- Patients will need to have at least 90 days baseline (i.e., a minimum 90 days of activity/enrolment/assignment before first prescription of azilsartan medoxomil and at least 60 days (to be agreed upon mutually between IMS and Takeda) continuous follow-up
- After first azilsartan medoxomil prescription, we will follow patients with variable follow-up to the end of data availability, or the last patient follow-up/enrolment date, depending on which date comes first
- Patients with various missing data elements that hinder analysis (e.g., date of birth, gender) will be excluded
- Patients with no records in the database for at least six months before the index date will of course be excluded

Study period
Considering launch of azilsartan medoxomil in Germany in January 2012, we will include data going back to October 1, 2011 (January 2012 and 90 days prior to first index date) up to most recent available.

Continous observation
The check of continuous observation allows the assessment whether the patient was continuously managed by the physician also after a discontinuation of azilsartan medoxomil prescriptions and has not change the physicians or died. The following criterion will be applied:

- at least one record (visit, prescription, diagnosis) after the length of the last documented azilsartan prescription.

Definition of outcome variables

The definition of outcomes variables was defined with respect to:

1. use of azilsartan medoxomil in non-approved indications
2. concomitant use of other antihypertensive drugs
3. concomitant use with drugs that may cause a drug interaction
4. use in patients with renal or hepatic injury

- The number and proportion of patients with a one or more of the following medical conditions before azilsartan medoxomil exposure start (identified using ICD-10-CM coding; note: diagnoses until 4 digits are available in DA Germany; the final list will be discussed and agreed with Takeda):
    - Essential hypertension (ICD-10-CM I10)
    - Hypertension, except essential (ICD-10-CM I11-I15)
    - Congestive heart failure
    - Myocardial infarction
    - Decreased liver function, by: hepatic disease (ICD-10-CM K70-K77)
    - Renal disease, by: ICD-10-CM acute kidney failure and chronic kidney disease (N17-N19)
    - Kidney transplant (ICD-10-CM Z94.0)
    - Renal artery stenosis (ICD I70.1)
- Number and proportion patients with liver function tests (AST, ALT) 3-time above normal value within one year before exposure start to azilsartan medoxomil (needs feasibility check)
- The number and proportion of with antecedent hypertension therapy
- The number and proportion of patients with azilsartan medoxomil mono- and combination therapy
- The number and proportion of patients with concomitant use of prescribed drugs which may cause a drug interaction: lithium, direct renin inhibitors (aliskiren), potassium-sparing diuretics, salt substitutes containing potassium, heparin.
- Azilsartan medoxomil treatment patterns. Treatment patterns will be described as sequences of treatment episodes. The first azilsartan medoxomil initiation, add-on, any therapy switch to azilsartan medoxomil observed within the study period will define the start of a treatment episode. Treatment information will include:
    - Index dose
    - Average daily dose
    - Number of first-time users

- Angiotensin converting enzyme inhibitors (ACE inhibitors) co-medication among azilsartan medoxomil prescribed patient cohort
- Other angiotensin receptor blocker (ARB) co-medication among azilsartan medoxomil prescribed patient cohort
- Other antihypertensive drugs (diuretics, beta blockers, alpha blockers, calcium antagonists)

Definition of other variables

- Patient demographics: age and gender, with age as follows:
  - <18
  - 18-75
  - ≥75

All the codes identified in the project will be listed in the Appendix of the Analysis Plan, and validated and approved by Takeda before proceeding with the analyses.

Analyses

Data will be analyzed using SAS software.

All data will be analyzed per the agreed upon Analysis Plan.

IMS statisticians will identify and extract the relevant data, develop the study matrix and study cohort. The statistical analysis will be done descriptively. Descriptive tables will be made for all variables. Continuous variables will be presented with counts, means, medians and standard deviation. Categorical variables will be presented in frequency tables. Confidence intervals will be provided when relevant. Where appropriate (to be agreed with Takeda and described in the statistical analysis plan), testing for differences between groups will be undertaken (t-test, Chi-square). Missing values will be reported as missing and no imputation will be conducted. The standard format will be two-way tables including totals having cohort or subgroups in columns and analysed variables in rows.

Results will be stratified by mono- and combination therapy and dosage at index where applicable.

A few notes:

- The number and proportion of patients with a one or more of the medical conditions listed above will be calculated overall, pre-index, and post-index.
- Antecedent non azilsartan medoxomil hypertension therapy will include hypertension therapy up to 90 days pre-index date.
- The index dose is defined as the dose of the index Edarbi drug
- Each prescription record includes a start date (=date of prescription), the quantity prescribed and the daily dose ('Tagdos'). In cases where the 'Tagdos' variable is missing, the normal daily dose will assumed to be equal to the mode of the distribution of the normal daily dose observed in the study population for the same substance, same strength and same formulation.
- For each prescription, the "prescription end date" (i.e. the end of prescription

coverage) will be calculated by adding up the estimated coverage (= number of units prescribed/Tagdos) to the prescription date.

- Co-medication will take into account all the medications recorded from 30 days pre-index until disruption of Edarbi treatment for more than 30 days (or end of data availability).
- Death records are not available.
- Before liver functions tests (AST, ALT) can be considered for analysis a feasibility check is necessary to identify the number of patients eligible for analysis. Based on previous experiences about 25% of patients can be expected.

Statisticians will perform the necessary data quality checks/assurance.

Sample size

This is a descriptive study of drug usage without any pre-defined hypothesis to be tested. Therefore, power calculation is not required. The current study will include and use all available patients that meet study selection criteria.
However, to guide expectations on the interpretation of results, IMS will conduct, as part of the project, sample precision estimates on of the least and most prevalent morbidity endpoints (e.g., hypotension in the eldery with prevalence of 5-33%ii).

Additionally, IMS already conducted an initial analyses of sample size of azilsartan medoxomil; in the period January 2012-December 2013 the total number of unique patients with at least one prescription of azilsartan medoxomil at time of analysis (February 2014) was 1156 patients in the GP panel (final sample size in study may vary based on in- and exclusion criteria applied).

Engagement description in more detail

A. Study Analysis Plan

Prior to commencing the data analyses, IMS will develop and, jointly with Takeda, finalise clearly defined objectives, methodological approaches and statistical analysis to undertake in an analysis plan. An analysis plan synopsis will be developed first, including patient selection criteria and objectives. Listings of tables (in excel) subsequently will be prepared based on analyses agreed upon and signed-off by Takeda prior to start of analysis.

For further information on the studied drug, the SPCs valid at the time of analysis plan finalisation will be included in the analysis plan.

IMS will be in charge of the documents preparation, submission and follow-up to fulfill legal/ethics requirements in database use if applicable for the study set up; the current scope of work only includes German where no additional legal/ethics requirements need to be fulfilled. No ethics committee (EC) review is required in Germany.

Should Takeda already have an approved Analysis Plan, then this Plan will be shared with IMS and IMS will make adjustment to specificities of IMS DA data which will be used in the current study.

B. Data Extraction and Analyses of Database

IMS statisticians will identify and extract the relevant data, develop the study matrix and study cohort and populate the agreed output tables and perform the necessary data quality checks/assurance. Calculations will be conducted by experienced statisticians in accordance with the approved Study Analysis plan.

C. Database Analyses

Analyses will be conducted per the study Analysis Plan.

D. Reporting

Results of analyses will be reported in the Microsoft Excel spreadsheet.

Following completion of all analyses, a study summary report will be prepared that will document the methods, data, analyses, and primary findings of the study. This report will be sent to Takeda for review and comments, after which it will be revised (as necessary) and finalised.

- In summary, deliverables for the project will include:
- Kick off meeting minutes
- Final study analysis plan
- Microsoft Excel spreadsheet with results; currently one round of analyses, one report per round (year 1 and year 5)
- Final summary report in Word; currently one rounds of analyses, so one report per round (year 1 and year 5)
- Report summary in PowerPoint; currently one rounds of analyses, so one report per round (year 1 and year 5)

Study strength and limitations

Study strength
Given that outcomes and exposure are based on routinely collected and recorded data, this study will give a real-life description of outpatient azilsartan medoxomil use in Germany.

Data used in the analyses are GPs' extracts of their EMRs therefore presenting a reflection of real-life treatment and diagnosis by the GP.

IMS DA GP panel data have a relative small availability lag time of 6 week.

Information on validity of the database is published by Becher et al.[iii]

The IMS DA databases are relied on by NICE and EMA. IMS DA databases (France, Germany, UK) are being relied on and used by the Pharmacovigilance and Risk Management Department of EMA for use in multiple analytical assessments including drug utilization and benefit/risk studies. And, IMS DA UK data have been used in the NICE commissioning guide on heart failure (http://publications.nice.org.uk/services-for-people-with-chronic-heart-failure-cmg39/determining-local-service-levels-for-a-chronic-heart-failure-service#ftn.footnote_20).

Study limitations

For the current study proposed GP data only will be included. Patients who switch GP or have a visit to a specialist cannot be tracked across GPs or from GP to specialist and as such this information would be missing. Therefore, co-medication includes medication prescribed by GP only (which may have been initiated by a specialist).

Due to the requirement that all patients should have a minimum of 6 months history, in order to evaluate clinical characteristics of interest, selection bias may occur. However, it is not likely that selection bias would be of significant impact as it is expected that ≥85% of patients will fulfil this criterion.

Relevant IMS Experience

Examples of work done before in this area when specifically using IMS DA Germany are given in Appendix B, References Section.[iv,v,vi,vii,viii,ix,x,xi]

IMS RWE/HEOR is a member of the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance.

Project Management

A. Project management details

- The project will be managed by the IMS Centre of Excellence (COE) in Epidemiology, Safety and Risk Management.
- Birgit Ehlken will be in charge of the project acting as project lead and QC reviewer
- Statistical analysis will be conducted by our in-house experts and aligned teams. These teams have many years combined experience of analysing and drawing statistically robust findings from longitudinal patient data.

During the project kick-off meeting we will discuss Takeda's preferred format and frequency for project status updates and other project-related communications. IMS recommends conducting both planned and ad hoc conference calls as needed with the Takeda project team throughout the project engagement. Prior to each planned teleconference, IMS will provide an email with suggested agenda items. Afterwards, we will follow-up with a top-line summary email reflecting main discussion points, decisions made, and action items resulting from the call. In-person meetings and supplementary conference calls will be scheduled as needed and on-going email communication between IMS and Takeda will occur throughout the project. During regularly scheduled and ad hoc calls, IMS will address any questions or concerns expressed by Takeda and IMS will discuss any task-related activities which require further clarification.

Appendix A: References

[i] H. Becher, K. Kostev and D. Schröder-Bernhardi. Validity and representativeness of the "Disease Analyzer" patient database for use in pharmaco - epidemiological and pharmacoeconomic studies. International Journal of Clinical Pharmacology and Therapeutics, Vol. 47 – No. 10/2009 (617-626).

[ii] Verhaeverbeke I, Mets T. Drug-induced orthostatic hypotension in the elderly: avoiding its onset. Drug Saf. 1997 Aug;17(2):105-18.

[iii] H. Becher, K. Kostev and D. Schröder-Bernhardi. Validity and representativeness of the "Disease Analyzer" patient database for use in pharmaco - epidemiological and pharmacoeconomic studies. International Journal of Clinical Pharmacology and Therapeutics, Vol. 47 – No. 10/2009 (617-626).

[iv] Kostev K, Haas G, Richter H. Datenbankbasierte Untersuchung zur Inzidenz der koronaren Herzkrankheit (KHK) bei Typ-2-Diabetes-Patienten in Deutschland Monitor Versorgungsforschung 2012 Feb (01)

[v] Stelzner F, Kostev K, Dippel FW. Inzidenz kardiovaskulärer Ereignisse bei Typ-2-Diabetes Patienten unter realen Versorgungsbedingungen: Vergleich zwischen Insulinglulisin und Normalinsulin. Monitor Versorgungsforschung 2012 Jan. (01): 29-33.

[vi] Krobot KJ, Wagner A, Siebert U. Risk factor levels, risk factor combinations, and residual coronary risk: population-based estimates for secondary prevention patients using statins. Eur J Prev Cardiolog. 2012 Feb;19(1):109-17. Epub 2011 Feb 14.

[vii] Breitscheidel L, Ehlken B, Kostev K, Oberdiek MS, Sandberg A, Schmieder RE. Real-life treatment patterns, compliance, persistence, and medication costs in patients with hypertension in Germany. J Med Econ. 2012;15(1):155-65. Epub 2011 Nov 8.

[viii] Kaiser E, Klebs S, Lied T, Sieder C, Kostev K, Mathes J, Fuchs S. A database analysis to evaluate the risk of cardiovascular events in hypertensive patients being treated with either the single pill combination of valsartan and amlodipine or the respective free Combination. Journal of Hypertension Vol 29, e-Supplement A, June 2011 [Poster on 21st European Meeting on Hypertension and Cardiovascular Prevention 2011]

[x] Mathes J, Kostev K, Gabriel A, Pirk O, Schmieder RE. Relation of the first hypertension-associated event with medication, compliance and persistence in naïve hypertensive patients after initiating monotherapy. Int J Clin Pharmacol Ther. 2010 Mar;48(3):173-83.

[xi] Tyczynski JE, Oleske DM, Klingman D, Ferrufino CP, Lee WC. Safety assessment of an anti-obesity drug (sibutramine): a retrospective cohort study. Drug Saf. 2012 Aug 1;35(8):629-44.