Del. 4.b
Final study protocol

for service contract

EMA/2011/38/CN - PIOGLITAZONE

V4.0
[Final]

May 20th 2012

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DOCUMENT INFORMATION

Tender ID	EMA/2011/38/CN		
Full title	Monitoring the effectiveness of risk minimisation in patients treated with **pioglitazone**-containing products		
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Status	Version 4.0	Final ☑
Nature	Report ☐ Protocol ☑	
Dissemination Level	Public ☐ Confidential ☑	

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DOCUMENT HISTORY

Name	Date	Version	Description
Vera Ehrenstein, Jørgen Rungby, Sinna Pilgaard Ulrichsen, Henrik Toft Sørensen	15/02/2012	1.0	First draft creation
Ingrid Leal, Susan Jick, Lin Li, Daniel Weibel, Miriam Sturkenboom	16/02 - 16/03	1.0	Internal review
Vera Ehrenstein	19/03/2012	2.0	Second draft
Susan Jick, Lin Li , Jørgen Rungby, Ingrid Leal, Daniel Weibel, Peter Rijnbeek, Lorenza Scotti, Ángel Honrado	19/03-30/03	2.0	Internal review
Vera Ehrenstein, Ángel Honrado	02/04/2012	3.0	Final version
Madalena Arriegas, Kevin Blake	02/04 - 24/04	3.0	EMA assessment
Vera Ehrenstein	25/04 - 10/05	3.1	Review and third draft creation
Susan Jick, Lin Li , Sinna Pilgaard Ulrichsen, Jørgen Rungby, Ingrid Leal, Daniel Weibel, Peter Rijnbeek, Ángel Honrado	10/06 - 17/06	3.1	Internal review
Vera Ehrenstein, Ángel Honrado	20/06/2012	4.0	Final version

DEFINITIONS

- Participants in this tender are referred to herein according to the following codes:

  - **AUH-AS** Aarhus University Hospital (Denmark).Contractor
  - **BCDSP** Boston Collaborative Drug Surveillance Program (USA). Subcontractor
  - **EMC** Erasmus University Medical Center (Netherlands). Subcontractor
  - **SYNAPSE** Synapse Research Management Partners S.L. (Spain). Subcontractor

- **Contract**: Legal document signed between the Contractor and the European Medicines Agency for the undertaking of the tender.
- **Contractor**: A tenderer to which a framework contract has been awarded and signed with the EMA. It is responsible before the EMA of the right execution of the tender and of the delivery of the results in due time and form according to the Contract.
- **EMA:** European Medicines Agency.
- **Subcontractor**: Organisation supporting the Contractor in the fulfilment of the tender objectives and technical execution.
- **Technical specifications**: Official document generated by the EMA for the tender that includes a detailed description of all technical requirements, contractual arrangements, and price, that enables the EMA to specify and acquire services provided by resources not employed directly by the EMA.
- **Tender**: Public (or restrictive) offer made by the EMA to specific providers to enter into the contract of transaction of services at certain specified cost.
- **Work plan**: Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in the Contract.

1. BACKGROUND AND RATIONALE

Pioglitazone belongs to the drug class thiazolidinediones and is used as a second-line therapy in patients with type 2 diabetes mellitus.[1] Pioglitazone was approved for use in the European Union in 2000. The drug controls type 2 diabetes in certain patients in whom traditional glucose-lowering drugs are not effective. Evidence suggests that the drug is associated with a slightly increased risk of bladder cancer.[2] Based on that evidence, on 21 July 2011, the EMA's Committee for Medicinal Products for Human Use (CHMP), concluded that 'although there is a small risk of bladder cancer with pioglitazone, its benefits continue to outweigh its risks in a limited population of type 2 diabetes patients'.[3] The Committee recommended discontinuation of pioglitazone in patients with bladder cancer or uninvestigated haematuria and in patients not deriving sufficient therapeutic benefit from pioglitazone; there is also a recommendation for consideration of patients' risk factors for bladder cancer, such as age and smoking, before initiating pioglitazone treatment; and for prescribing the lowest possible dose to elderly patients.[3] Following the CHMP recommendation, Takeda UK Ltd., the marketing authorization holder for pioglitazone, issued a "Dear Health Professional" communication (DHPC), detailing the labelling amendments.

This study was commissioned by the EMA. EMA wishes to assess, in two or more European Union Member States, changes in pioglitazone utilization and patient-level outcomes following the DHPC, including size and composition of the treated patient population. On the patient level, EMA wishes to assess diabetes control among patients who remained on or discontinued pioglitazone drug after the DHPC.

2. OBJECTIVES

The four objectives of this study, listed below, relate to the effects of pioglitazone DHPC on the utilization of pioglitazone-containing products (Objective 1) and on patient-level diabetes control (Objective 2). Objective 3 and Objective 4 relate to interpretation and reporting of results obtained by addressing Objective 1 and Objective 2. Fulfilment of Objective 3 and Objective 4 is described in **Section 5.5 Reporting and dissemination of results.**

- **Objective 1**: To provide observational data on drug utilisation patterns of pioglitazone-containing products in the European Union (EU) and to study associations between changes in drug utilisation patterns and the regulatory decisions in the form of DHPC.
- **Objective 2a**: To analyse events in patients discontinuing pioglitazone after the DHPC, including adverse drug events, alterations in glycaemic control, and modification of other objective parameters of disease.
- **Objective 2b**: To analyse contraindications and events in patients continuing or starting pioglitazone, including adverse drug events, alterations in glycaemic control, and modification of other objective parameters of disease.
- **Objective 3.** To evaluate effectiveness of risk minimisation measures recommended by CHMP based on results obtained for Objective 1 and Objective 2.
- **Objective 4.** To provide practical recommendations for improving effectiveness of risk minimisation measures.

3. METHODS

3.1 SOURCE POPULATION AND STUDY POPULATION

The source population for this study will be residents of three EU Member States covered by relevant medical databases (described in **Section 7 Data sources**). In Denmark, the source population for the analysis of utilization will include the entire study population from 2004 to 2011; for the analysis of laboratory data, the analysis will be restricted to residents of the North and the Central Denmark regions, represented by the Aarhus University Research Database (AU), which includes information on laboratory data[4,5]; in the Netherlands, residents treated by general practitioners participating in the Integrated Primary Care Information (IPCI); and in the United Kingdom, patients treated by general practitioners participating in the General Practice Research Database (GPRD).[6,7]

The study population will be members of the source population with an identifiable record of use of pioglitazone-containing products. Hereafter 'pioglitazone use' refers to use of all pioglitazone-containing products, unless stated otherwise. Only patients with at least one year of recorded data in the database before the first time pioglitazone use will be included in the study.

3.2 STUDY DESIGN AND STUDY PERIOD

For Objective 1, we will conduct a drug utilization study to examine utilization of pioglitazone over time, and changes in utilization patterns in relation to DHPC. For Objectives 2a and 2b, we will use the historical cohort design to provide descriptive analysis of the occurrence of potential adverse events and changes in objective parameters of disease among pioglitazone users.

The study period will begin on 1.1.2000 in GPRD, on 1.1.2004 in Denmark, and on 1.1.2007 in IPCI, reflecting availability of prescription data. The end of observation will be determined by the status of database updates (see **Section 7 Data sources**) and will vary by country.

Data cut: the final report will contain data updated and available in the three databases as of 1 August 2012. On that date, all three databases are expected to have data on pioglitazone utilization at least through the end of 2011.

3.3 EXPOSURE

3.3.1 Initiation, use, and termination of pioglitazone-containing products

New user of pioglitazone will be defined as a person with the first recorded prescription for a pioglitazone-containing product in the absence of such prescriptions at least 6 months before the date of the first pioglitazone prescription. The date of the first-recorded pioglitazone prescription will be the date of the initiation of pioglitazone. This date will be used as baseline for ascertaining baseline characteristics among new users of pioglitazone.

Prevalent user of pioglitazone is a pioglitazone user who had initiated pioglitazone before a given date and continues to be on the drug, as evidenced by the date of the most recent prescription and the estimated prescription length.

Prescription length will be defined separately in each database, based on prescribing practices and the best available data. In the AU databases the prescription length for each prescription will be the number of days supplied based on the number of defined daily doses (DDD) in a dispensed prescription. In the IPCI database, prescribed dose will be used whenever recorded; if not recorded, DDD will be used. In the GPRD, prescription length for pioglitazone, based on recommendation and actual use.

Last prescription for pioglitazone will be defined as the prescription for pioglitazone product followed by absence of a new prescription for a pioglitazone for 2 or more prescription lengths, or end of the patient record, whichever comes first. The end of patient record occurs by death, migration from the database catchment area, or end of study.

Termination of pioglitazone will be defined as the date of the last estimated drug intake, calculated by adding the estimated prescription length to the date of the last prescription for a pioglitazone-containing product. If death, emigration, or the end of the follow-up occurs before the end of the estimated prescription length, the date of death, emigration, or end of follow-up will be recorded as date of termination of pioglitazone.

DHCP baseline (or DHPC) is the calendar date of the "Dear Health Professional" communication **(DHPC)**. This date will be used as the baseline date of utilization patterns among prevalent users of pioglitazone at the time of DHPC. The country-specific **DHPC** baselines are:

DENMARK	11 August 2011
NETHERLANDS	05 August 2011
UNITED KINGDOM	29 July 2011

These dates were communicated in an email from 20 February 2012 by the following official:

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3.4 ENDPOINTS

3.4.1 Utilization patterns

Changes in utilization of pioglitazone over time will be reported for the number of new users, prevalent users, and the number of prescriptions during the study period. First, we will report baseline characteristics of new users of pioglitazone containing products before and after the country-specific date of DHPC. The data will include type of first pioglitazone-containing product prescribed; calendar year of pioglitazone initiation; sex; age at pioglitazone initiation, contraindications (heart failure, hepatic impairment, diabetic ketoacidosis, bladder cancer, any recorded haematuria); diabetes-related characteristics (glycated haemoglobin A [HbA1c]; fasting plasma glucose [FPG]; duration of type 2 diabetes); overall comorbidity (measured by Charlson comorbidity index); history of medication use (lipid-lowering agents, antihypertensive agents, diuretics; nitrates; antiplatelet agents); and lifestyle factors whenever available (obesity, defined as body mass index ≥30 kg/m^2 or a relevant diagnostic codes; smoking, alcohol use).

The look-back period for assessment of the baseline covariates will be based on the period covered by each database and by clinical relevance. History of cancer, and Charlson comorbidity index, medication use, obesity, smoking and alcoholism will be assessed using the entire period available in each database. Diabetes-related characteristics will be assessed within up to 24 months before the baseline. Measurable characteristics will be database-specific. Duration of diabetes will be defined as the time from diabetes onset until pioglitazone initiation date. Diabetes onset will be defined as the date of the first prescription for an oral hypoglycaemic agent or the date of the first-recorded diabetes diagnosis.

Concomitant treatment of pioglitazone with other glucose lowering agents will be assessed among new users of pioglitazone before and after DHPC. Among the new users, we will define the on-treatment period starting from the date of the first prescription of pioglitazone and ending at the end of the last prescription for pioglitazone (or end of the follow-up). Presence of concomitant treatment with glucose-lowering agents will be defined as at least one prescription for a given agent recorded during the on-treatment period. Pioglitazone combination preparation with metformin, glimepiride or alogliptin will be reported as concomitant treatment with the respective oral glucose lowering agent.

To assess switching to and from alternative therapies, among all new users of pioglitazone, we will report distribution of last glucose-lowering agent(s) prescribed before the initiation of pioglitazone. Among patients who terminate pioglitazone not as a result of death emigration or end of follow-up, we will report the distribution of the first glucose-lowering agent(s) prescribed after termination of pioglitazone.

To examine changes in pioglitazone utilization around the time of DHPC, we will identify a cohort of prevalent users of pioglitazone, i.e. those who started the drug before the DHPC date and a cohort of new pioglitazone users, ie those who started the drug on or after the DHPC date. The baseline among the prevalent users will be the DHPC date. The baseline for the new users will be the initiation date. We will examine:

- Prevalence of contraindications and risk factors for bladder cancer separately for the prevalent users and for the new users, by calendar month starting in July 2011 and until the end of the follow-up.
- To examine how investigation of haematuria affected utilization of pioglitazone, we will report the number and the proportion of the prevalent pioglitazone users with a haematuria record after DHPC, and among those, the number and proportion of patients subsequently terminating pioglitazone. Among patients initiating pioglitazone after DHPC, we will examine the proportion of those with haematuria recorded after DHPC but before pioglitazone initiation.
- To assess whether periodic reviews of treatment took place, we will count, for each of the cohort members, the number of HbA1c measurements recorded from DHPC and until the end of the follow-up (for prevalent users) or from the first pioglitazone prescription until the end of the follow-up (for new users initiating after DHPC). We will report the distribution of the total number of the post-DHCP/post-initiation HbA1c measurements in this cohort (0, 1, >1).
- To assess outcomes of periodic treatment reviews we will identify patients failing to derive sufficient benefit from treatment. Failure to derive treatment benefit will be defined as at least one measurement of HbA1c ≥7.5% recorded after DHPC (for prevalent users) or the initiation of pioglitazone (for new users). Among the patients identified as failing to derive sufficient treatment benefit, we will report the proportion receiving at least one prescription for pioglitazone after the date of the recorded HbA1c≥7.5%. We will also assess the proportion of prevalent (as of DHPC date) pioglitazone users who discontinue pioglitazone treatment after DHPC date in the absence of evidence of insufficient treatment benefit (patients without data on HbA1c or patients with HbA1c <7.5%).

To compare prescribing patterns in the elderly before and after DHPC, we will compare new users of pioglitazone before DHPC with new users of pioglitazone after DHPC with respect to

- Age distribution at the start of pioglitazone therapy;
- First prescribed dose, stratified by age group. First prescribed dose will be estimated by dividing the total amount of pioglitazone dispensed at the initiation date by the time between the first and the second prescription for pioglitazone.
- Prevalence of concomitant use of pioglitazone with insulin by age group. Concomitant use with insulin will be defined as record of at least one prescription for insulin between the first-recorded and the last-recorded prescription for pioglitazone.

3.4.2 Patient-level endpoints

Patient-level outcomes will be examined in the following two groups of patients: 1) all users of pioglitazone on/after DHCP (new and prevalent users combined); and 2) persons terminating pioglitazone after DHCP (group 2 is a subset of group 1).

For the analysis of the prevalent/new users, baseline will be defined as the date of DHCP (for prevalent users) or date of the first prescription for pioglitazone after DHCP (for new

users). For the analysis of terminating patients, baseline will be defined as the date of termination of pioglitazone.

Potential adverse events

We will examine occurrence of the following potential adverse events during the relevant follow-up, separately for prevalent/new and for terminating users:

- Death from all causes;
- Diabetes complications, defined as a compound outcome of acute renal failure, diabetic coma, or diabetic acidosis;
- Cardiovascular events, defined as a compound outcome of acute myocardial infarction, acute coronary syndrome, any stroke.

The follow-up will start on the date of the relevant baseline and will at the earliest of 45 days, death (for diabetic complications and cardiovascular events).

Measures of diabetes control

This analysis will be conducted using available data on laboratory tests in the three databases. In AU, laboratory data analysis will be restricted to users of pioglitazone in northern Denmark, the area covered by the clinical laboratory information systems (the LABKA database[4]).

Glycated haemoglobin A (HbA1c) and fasting plasma glucose (FPG) will serve as measures of glycaemic control. Whenever available, renal function will be measured using estimated glomerular filtration rate (eGFR), calculated based a standard formula using serum creatinine, age and sex. Serum creatinine measurement used for this calculation can occur any time during the relevant follow-up. Lipids will be measured by fasting serum concentrations of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.

Pre- and post-baseline values in these parameters will be compared for new/prevalent post-DHPC users and for post-DHPC terminators. The baseline value of a laboratory parameter will be the value most proximal in time to the DHCP baseline /termination date measured during the preceding 24 months. Changes in all laboratory parameters except eGFR will be assessed at 3, and 6 months post-baseline. These periods will be defined to provide non-overlapping, all-inclusive continuity of observation, with each period continuing until the time accumulated for the next period, as follows: >0-3 months=1–179 days; >3-6 months=180–359 days. Within each period, the earliest available post-DHPC/termination measurement will be used for the follow-up value. EGFR will be assessed at the first available measurement during the follow-up.

3.5 ANALYSIS PLAN

We will report prevalences and distributions of variables in the descriptive utilization tables (e.g., prevalence of users with history of bladder cancer, distribution of age groups). For adverse events, we will report incidence rates with 95% confidence intervals. For changes in the laboratory parameters, we will report means or medians, or both, as appropriate based on underlying distributions; with appropriate measures of spread. This report will

contain descriptive analyses. No hypothesis will be tested. Appendix 1 and Appendix 2 list suggested tables and figures to be included in the report.

4. SOURCE OF BIAS AND LIMITATIONS

The main types of systematic error in epidemiologic studies include selection bias, information bias and confounding. Because of routine data collection in the data sources involved, selection bias is expected to be negligible. Information bias may stem from inability to ascertain the actual drug intake from prescription issue or dispensation data; however, because diabetes is a chronic condition requiring treatment – including pioglitazone - high compliance with all glucose-lowering drugs will be assumed. It is acknowledged that exact timing of start and end of medication intake will inevitably be misclassified to a certain extent. This is general limitation of drug safety studies. These sources of bias will be explicitly discussed in study reports and will be considered when interpretation of the study findings.

Uninvestigated haematuria is an important DHPC contraindication for continuing or starting pioglitazone. We will not be able to quantify this in these databases. We will, however, be able to capture the presence of haematuria though with unknown completeness. It can be indirectly inferred that for patients with a haematuria record, in whom pioglitazone was stopped, the haematuria was significant and considered a potential early sign of bladder cancer. However, in these patients, termination of pioglitazone for other – possibly unmeasured reasons – cannot be ruled out based on the available data.

While results of this investigation may be assumed generalisable to the populations of pioglitazone users in Denmark, the Netherlands, and the United Kingdom, generalisability to the entire EU population is less clear. To assess generalisability, we obtain all published data on pioglitazone utilization in other EU Member States and use that information when interpreting results of the present study.

5. QUALITY ASSURANCE, FEASIBILITY AND REPORTING

5.1 DATA STORAGE

Due to the differences in the statistical software and analytical capabilities across the institutions, a distributed network approach will be adopted in this project. JERBOA © is custom built JAVA-based software created in the EU-ADR project[9] (FP7-ICT-215847) and that has been used in other European funded projects (i.e. VAESCO, SOS) will be used. Each database owner will locally create standardized input files (patients, events and prescriptions). JERBOA © aggregates, anonymises the information in those files and produce encrypted output files that will be shared and stored centrally for further analysis.

5.2 METHODS FOR QUALITY ASSURANCE

The core research team will consist of epidemiologists and biostatisticians with experience in drug safety studies; for clinical and laboratory data extraction, and results' interpretation, an experienced diabetologist will be consulted. Data linkage, extraction, coding, and management will be conducted by experienced statisticians and data managers, using established institutional facilities, including secure servers. The milestones for data collection, analysis, and final report submission have been established and agreed upon

with the Agency. A professional project managing company will provide administrative and communication support. A built-in quality assurance method is use of different databases to provide estimates of the same population parameters (drug utilization patterns, incidence rates of adverse events). Although certain level of inter-database variation is expected based on the true differences in the underlying population and in recording practices, overt discrepancies in results stemming from different databases will be flagged and investigated to assure quality.

5.3 DATA QUALITY

There were several validation studies of Danish registries, demonstrating adequacy of data quality for epidemiologic research.[5,10,11] Likewise, the GPRD was has been demonstrated to contain high-quality data.[6,7] The IPCI database has been validated and for its use in post-marketing surveillance, has proven to be useful for post-marketing surveillance, that purpose and has been used in other European funded projects (i.e. SOS - FP7-HEALTH-223495).[12]

5.4 FEASIBILITY AND TIMELINES

In Denmark, pioglitazone has been available since 2000 as a single-substance preparation (source: Danish Medicines Agency, www.dkma.dk). In The Netherlands, and in the United Kingdom, pioglitazone has been marketed as a single-substance preparation and in combination with glimepiride and/or metformin (sources: Medicines Evaluation Board, Medicines and Healthcare Products Regulatory Agency http://www.mhra.gov.uk). Based on this information, it is feasible to conduct this study using the listed databases.

The project will be implemented according to the following milestones/timelines:

MILESTONE	DATE OF COMPLETION
D4.a: Preliminary study protocol submitted to the Agency for a 15-day consultation period	20/05/2012
D4.b: Final study protocol revised after consideration of Agency's comments; the final study protocol shall be subject of an ENCePP seal application.	20/06/2012
D5.a: Interim report on study results of the epidemiological study, submitted to the Agency for a 15-day consultation period	20/11/2012
D5.b: Final report on study results of the epidemiological study.	20/02/2013
D3: Report with an evaluation of the impact of the recent regulatory decisions on the utilisation patterns of this drug and other anti-diabetic medications.	20/03/2013

5.5 REPORTING AND DISSEMINATION OF RESULTS

Reporting and dissemination of results will fulfil Objective 3 and Objective 4 of this study.

Objective 3 is provision of comprehensive and judicious interpretation of findings obtained while achieving Objective 1 and Objective 2. The findings will be presented in the form of a formal epidemiologic study report, and interpretation of results is an integral part of such a report. Effectiveness of risk minimisation on the population level will be evaluated by the proportion of persons with contraindications among pioglitazone users in relation to the timing of DHPC. Effectiveness of risk minimisation measures on individual level will be

evaluated based on stability of diabetes and by occurrence of potential acute adverse events in persons terminating and continuing pioglitazone after the DHPC. Precision of the estimates, risk of systematic error, and clinical significance of results will be considered when interpreting the findings.

Objective 4 is provision of practical recommendations for improving effectiveness of risk minimisation measures. Based on findings obtained while achieving Objective 1 and Objective 2 and their interpretation (Objective 3), practical recommendations will be formulated, in liaison with EMA, for improving effectiveness of risk minimisation measures in Europe. Particular care will be taken to interpret the data while weighing strengths and limitations of each piece of evidence, and accounting for potential sources of bias.

5.6 AMENDMENTS

An amendment of the existing contract becomes necessary anytime any of the contractual terms need to be changed (e.g., delivery dates of deliverables, modification of the contractor's address, etc.) without any constraint on either the time or the quantity. Amendments always should be requested based on reasoned justification that will be included in an email to be sent to the EMA, together with the proposed modifications.

The EMA gives its initial response by email. Time required for response will depend on the nature, complexity and scope of the proposed amendment. Once it has become clear that the amendment is necessary, the EMA drafts the 'contract amendment' reflecting the amendments to the existing contract and transmits the draft to the contractor for review; once agreed, the EMA prepares two copies of the amendment which are signed by the Agency's representative, and then transmitted to the contractor for counter-signature. One original copy remains with the contractor, the other original is returned to the Agency.

5.7 INDEPENDENT REVIEW OF STUDY RESULTS

Following ENCePP policies, the protocol of this study will be used to apply for an ENCePP seal. The Interim Report and the Final Report will be available in open-access format on the EMA's ENCePP register of studies.

As mandated by the ENCePP, interim and final reports of this investigation will be published in the ENCePP register of studies. Subsequently, reports will be submitted to appropriate peer reviewed journals.

6. ETHICAL ISSUES

This final study protocol will be submitted for an approval to the appropriate authorities: the Danish Data Protection Agency (Datatilsynet) for the AU database; the "Raad van Toezicht van IPCI" (Board of Supervisors) for the IPCI database, and by the Independent Scientific Advisory Committee of the GPRD (ISAC).

7. DATA SOURCES

The following table provides brief description of the three automated databases in the European Union that will be used to in this project.

CHARACTERISTIC	DATABASE		
	AU	IPCI	GPRD
Type of database	Population-based medical registries	GP database	GP database
Coding system for drugs	ATC	ATC	READ
Coding system for events	ICD-8, ICD-10	ICPC 1	READ
Free text	No	Yes	Available on request
Availability of FU years	Drugs 2003-2011; hospital visits 1977-2011, including outpatient visits since 1995	2007 up to date	1990 to 2011
Patient identifier used for linkage	The Danish Civil Registration System	Patient file	The GPRD administrative file
Deaths	The Danish Civil Registration system	Patient file	The GPRD event file plus death registry data where available.
Prescription medication	Aarhus University Prescription Database; reimbursed prescriptions filled in outpatient pharmacies	Prescriptions file: issued prescriptions	The GPRD drug file: issued prescriptions
Diagnoses	Inpatient and outpatient hospital-based diagnoses, recorded in the Danish National Registry of Patients	Diagnosis file (ICPC) and Journal (free text)	The GPRD event file
Laboratory tests	The Laboratory Information Systems research database	Measurements file and Journal (free text)	The GPRD laboratory file
Smoking, alcohol use body mass index	Hospital codes for obesity and alcohol use will be used	Diagnosis file and Measurements file	The GPRD registration file

8. REFERENCES

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9. APPENDICES

9.1 APPENDIX 1. PROPOSED TABLES/FIGURES FOR UTILIZATION ANALYSIS

Figure 1. New users of pioglitazone-containing products over calendar time, by database.
Figure 2. Prevalent users of pioglitazone-containing products over calendar time, by database.
Figure 3. Prescriptions of pioglitazone-containing products over calendar time, by database.

Year (year)	Month (month)	Number of new users* (starters of pio) (starters)	Number of terminators** (terminators)	Number of prevalent users*** (users)	Number of prescriptions for pioglitazone-containing products (all preparations) (prescriptions)
2000	1				
2000	2				
…					
2011	1				
2011	2				

Table 1.Baseline characteristics of the new users of pioglitazone who initiate pioglitazone before DHPC (baseline=initiation date).

CHARACTERISTIC	DATABASE		
	AU *(Northern Denmark)*	**IPCI** *(Netherlands)*	**GPRD** *(United Kingdom)*
All new users in period	N		
Type of pioglitazone preparation			
All preparations	N (XX.X%)		
Pioglitazone			
Pioglitazone and glimepiride			
Pioglitazone and metformin			
Pioglitazone and alogliptin			
Calendar year of pioglitazone initiation (all preparations)			
2000			
2001			
…			
2011			
Sex			
Men			
Women			
Age at initiation of pioglitazone-containing products, years			
<18			
18-35			
35-44			
45-54			
55-64			
65-74			
75-84			
≥85			
History of potential contraindications any time before initiation			
Any contraindication			

Bladder cancer				
Haematuria				
Mild hepatic impairment				
Moderate to severe hepatic impairment				
Diabetic ketoacidosis				
Heart failure				
Diabetes-related history in 24 months before initiation				
Glycated haemoglobin A (HbA1c), %, mean (SD)	XX.X (X.X)			
Inadequate glycaemic control (HbA1c ≥ 7.5%)				
Fasting plasma glucose, mmol/L, mean (SD)	XX.X (X.X)			
Duration of type 2 diabetes, months, mean (SD)				
Charlson comorbidity index any time before initiation				
Low (0)				
Medium (1-2)				
High (>2)				
History of medication use any time before initiation				
Lipid-lowering agents				
Antihypertensive agents				
Diuretics				
Nitrates				
Antiplatelet agents				
Lifestyle factors (whenever available)				
Obesity/ BMI				
Smoking				
Alcoholism				

Table 2.Baseline of the new users of pioglitazone who initiate pioglitazone after DHPC (baseline=initiation date).

SAME ROWS AND COLUMNS AS TABLE 1

Table 3.Concomitant treatment of pioglitazone with other glucose-lowering agents before DHPC (new users starting before DHPC).

CHARACTERISTIC	ATC CODE	DATABASE		
		AU *(Northern Denmark)*	**IPCI** *(Netherlands)*	**GPRD** *(U. Kingdom)*
Insulins and analogues	A10A	XXX (XX.X%)		
Biguanides	A10BA			
**list specific drugs in each category				
Sulfonamides, urea derivatives	A10BB			
Sulfonamides (heterocyclic)	A10BC			
Combinations of oral blood glucose lowering drugs	A10BD			
Alpha glucosidase inhibitors	A10BF			
Thiazolidinediones	A10BG			
Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH			
Alpha glucosidase inhibitors	A10BF			
Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH			
Other blood glucose lowering drugs, excl. insulins	A10BX			

Table 4.Concomitant treatment of pioglitazone with other glucose-lowering agents after DHPC (new users starting after DHPC).
SAME ROWS AND COLUMNS AS TABLE 3.

Table 5. Distribution of last glucose-lowering drugs prescribed before the initiation pioglitazone (all new users).
SAME ROWS AND COLUMNS AS TABLE 3.

Table 6. Distribution of first glucose-lowering drugs prescribed after termination of pioglitazone (all terminating users).
SAME ROWS AND COLUMNS AS TABLE 3.

Table 7. Prevalence of contraindications and risk factors for bladder cancer among prevalent users of pioglitazone at DHPC.

	MONTH, 2011					
	July	**August**	**September**	**October**	**November**	**December***
Contraindication						
Heart failure						
Mild hepatic impairment						
Moderate or severe hepatic impairment						
Diabetic ketoacidosis						
History of bladder cancer						
Haematuria						
Risk factors for bladder cancer						
Age at first pioglitazone prescription (categories)						
History of smoking						

Table 8. Prevalence of contraindications and risk factors for bladder cancer among new users of pioglitazone after DHPC.
SAME ROWS AND COLUMNS AS TABLE 7

Table 9. Estimated first prescribed dose among new users of pioglitazone, before DHCP, by age group

	AU	IPCI	GPRD
	N=		
	Estimated first dose, median (quartiles)		
Age group, years			
<50	Median (quartiles)		
50-<55			
55-<60			
60-<65			
65-<70			
70-<75			
75-<80			

Table 10. Estimated first prescribed dose among new users of pioglitazone, after DHCP, by age group
SAME ROWS AND COLUMNS AS TABLE 9

Table 11. Prevalence of concomitant use with insulin, new users before DHPC, by age group

	AU	IPCI	GPRD
	N=		
	Number (%)		
Age group, years			
<50	N (%)		
50-<55			
55-<60			
60-<65			
65-<70			
70-<75			
75-<80			

Table 12.Prevalence of concomitant use with insulin, new users after DHPC, by age group
SAME ROWS AND COLUMNS AS TABLE 11

9.2 APPENDIX 2. PROPOSED TABLES FOR PATIENT-LEVEL OUTCOMES

Table 13. Potential adverse events and among prevalent and new users of pioglitazone after DHPC within 45 days of baseline. Baseline=DHPC/initiation date.

ADVERSE EVENT	DATABASE								
	AU			IPCI			GPRD		
	N at risk	Events	Risk (95% CI)	N at risk	Events	Risk (95% CI)	N at risk	Events	Risk (95% CI)
Death of all causes									
Diabetes complications									
Acute cardiovascular event									

Table 14. Potential adverse events among persons terminating pioglitazone after DHCP, within 45 days of termination, by database/country. Baseline = termination date.
SAME ROWS AND COLUMNS AS TABLE 13

Table 15. Changes in laboratory parameters before and after DHPC among prevalent and new users of pioglitazone at DHPC (Baseine=DHPC/initiation date).

	AU		IPCI		GPRD	
	3 months	6 months	3 months	6 months	3 months	6 months
HbA1c, %						
N with both measurements	XX					
Baseline mean (SD)	Xx (xx)					
Follow-up mean (SD)						
Change from baseline, mean (95% CI)						
FPG, mmol/L						
N with both measurements						
Baseline mean (SD)						
Follow-up mean (SD)						
Change from baseline, mean (95% CI)						
Total cholesterol, mmol/L						
N with both measurements						
Baseline mean (SD)						
Follow-up mean (SD)						
Change from baseline, mean (95% CI)						
HDL cholesterol, mmol/L						
N with both measurements						
Baseline mean (SD)						
Follow-up mean (SD)						
Change from baseline, mean (95% CI)						
LDL cholesterol, mmol/L						
N with both measurements						
Baseline mean (SD)						
Follow-up mean (SD)						
Change from baseline, mean (95% CI)						
Triglycerides mmol/L						

N with both measurements			
Baseline mean (SD)			
Follow-up mean (SD)			
Change from baseline, mean (95% CI)			
	First measurement after baseline	**First measurement after baseline**	**First measurement after baseline**
eGFR			
N with both measurements			
Baseline mean (SD)			
Follow-up mean (SD)			
Change from baseline, mean (95% CI)			

Table 16. Changes in laboratory parameters before and after pioglitazone termination among patients terminating pioglitazone after DHPC. Baseline=date of termination.
SAME ROWS AND COLUMNS AS TABLE 15

9.3 APPENDIX 3. ALGORITHMS USED TO IDENTIFY STUDY VARIABLES

9.3.1 Algorithms for AU Database

DISEASE/CONDITION	ICD-8 CODE (1977-1993)	ICD-10 CODE (1994-)
Diabetes type 2	250.00; 250.06; 250.07; 250.09	E11.0; E11.1; E11.9
Cancer of bladder		C67
Haematuria	N/A	R31 Haematuria, unspecified
Mild hepatic impairment	571, 573.01, 573.04	B18, K70.0–K70.3, K70.9, K71, K73, K74, K76.0
Moderate to severe hepatic impairment	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00–456.09	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
Acute myocardial infarction	410	I21-I23
Acute coronary syndrome	410, 413	I20-I24
Ischemic heart disease	410-414	I20-I25
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49;	I50, I11.0, I13.0,I13.2
Acute renal failure	N/A	N17
Diabetic coma	N/A	E10.0, E11.0, E12.0,E13.0, E14.0
Diabetic acidosis	N/A	E10.1, E11.1, E12.1,E13.1, E14.1
Alcoholism	291, 303, 577.10, 571.09, 571.10	F10.1-F10.9, G31.2, G62.1, G72.1, I42.6, K29.2, K86.0, Z72.1
Obesity	277.99	E65-E66

Diagnostic codes used to compute Charlson Comorbidity Index[13]

	DISEASE	ICD-8 CODE	ICD-10 CODE	SCORE
1	Myocardial infarction	410	I21;I22;I23	1
2	Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2	1
3	Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70; I71; I72; I73; I74; I77	1
4	Cerebrovascular disease	430-438	I60-I69; G45; G46	1
5	Dementia	290.09-290.19; 293.09	F00-F03; F05.1; G30	1
6	Chronic pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3	1
7	Connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86	1
8	Ulcer disease	530.91; 530.98; 531-534	K22.1; K25-K28	1
9	Mild liver disease	571; 573.01; 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0	1
11	Hemiplegia	344	G81; G82	2
12	Moderate to severe renal disease	403; 404; 580-583; 584; 590.09; 593.19; 753.10-753.19; 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61	2
14	Any tumour	140-194	C00-C75	2
15	Leukaemia	204-207	C91-C95	2
16	Lymphoma	200-203; 275.59	C81-C85; C88; C90; C96	2
17	Moderate to severe liver disease	070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85	3
18	Metastatic solid tumour	195-198; 199	C76-C80	6
19	AIDS	079.83	B21-B24	6

Anatomical Therapeutic Chemical (ATC) codes used to abstract the Aarhus University Prescription Database

DRUG	ATC CODE
Insulins and analogs	A10A
Biguanides	A10BA
Sulfonamides, urea derivatives	A10BB
Sulfonamides (heterocyclic)	A10BC
Combinations of oral blood glucose lowering drugs	A10BD
Alpha glucosidase inhibitors	A10BF
Thiazolidinediones	A10BG
Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH
Alpha glucosidase inhibitors	A10BF
Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH
Other blood glucose lowering drugs, excl. insulins	A10BX
Lipid-lowering drugs including statins	C10A
Antihypertensive agents	C07 beta blockers C08 calcium channel blockers C09 ACE-inhibitors
Diuretics (loop, potassium sparing, thiazide)	C03
Nitrates	C01DA
Antiplatelet agents (anti-thrombotic)	B01A

ATC classification: http://www.whocc.no/atc_ddd_index/

Codes used to identify laboratory tests according to the International Union of Pure and Applied Chemistry (IUPAC) and internal laboratory codes

TEST	IUPAC CODES/INTERNAL LAB CODES
Fasting plasma glucose	ASS00203, ASS00204, DNK35842, NPU02193, NPU02195, NPU08509, NPU08972, NPU22069
Glycated haemoglobin A (HbA1c)	NPU02307,NPU03835
Serum creatinine	NPU18016, NPU01807
Total cholesterol	NPU01566
LDL cholesterol	NPU01568, NPU10171
HDL cholesterol	NPU01567, NPU10157
Triglycerides	NPU03620

IUPAC codes: http://www.sst.dk/NPU

9.3.2 Algorithms for IPCI

DISEASE/CONDITION	ICPC 1	FREE TEXT
Diabetes type 1	T90	Yes
Diabetes type 2	T90	Yes
Cancer of bladder	U76	Yes
Haematuria	U06	Yes
Mild hepatic impairment	D97	Yes
Moderate to severe hepatic impairment	D97	Yes
Acute myocardial infarction	K75	Yes
Acute coronary syndrome	K74, K75	Yes
Ischemic heart disease	K74, K75, K76	Yes
Congestive heart failure	K77	Yes
Acute renal failure	U99	Yes
Diabetic coma	NA	Yes
Diabetic acidosis	NA	Yes
Alcoholism	P15, P16	Yes
Obesity	T82	Yes

Diagnostic codes used to compute Charlson Comorbidity Index

	DISEASE	ALGORITHM (ICPC CODE + FREE TEXT)	SCORE
1	Myocardial infarction	K75 + free text	1
2	Congestive heart failure	K77 + free text	1
3	Peripheral vascular disease	K92 + free text	1
4	Cerebrovascular disease	K90 + free text	1
5	Dementia	P70 + free text	1
6	Chronic pulmonary disease	R95 + free text	1
7	Connective tissue disease		1
8	Ulcer disease		1
9	Mild liver disease	D97 + free text	1
11	Hemiplegia	N18 + free text	2
12	Moderate to severe renal disease	U99 + free text	2
14	Any tumour	B74, D74, D75, D76, D77, F74, H75, K72, L71, N74, N76, R84, R85, S77, S79, S80, T71,T73, U75, U76, U77, U79, Y77, Y78, Y79 + free text	2
15	Leukaemia	B73 + free text	2

16	Lymphoma	B72 + free text	2
17	Moderate to severe liver disease	D97 + free text	3
18	Metastatic solid tumour	A79 + free text	6
19	AIDS	B90 + free text	6

9.3.3 Algorithms for GPRD

Included as a separate document (Annex I) due to document length.