PROTOCOL

A Study on the Utilization of Pioglitazone in Clinical Practice With Regard to Diabetic Treatment Regimen and Comorbidities

Adapted Protocol Describing Analyses by PHARMO Institute for Drug Outcomes Research

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

EMA	European Medicines Agency
CED	Cohort Entry Date
GP	General Practitioner
ICPC	International Classification of Primary Care
HbA1c	glycosylated hemoglobin
ORF	Observational Research File
SmPC	Summary of Product Characteristics

1.0   SUMMARY

The goal of this study is to describe the prescription of pioglitazone in diabetic patients according to Summary of Product Characteristics (SmPC), and to evaluate the implementation of the risk minimization measures introduced in July 2011 regarding bladder cancer and heart failure and the need for regular review of the benefits of therapy. This drug utilization study will describe the pioglitazone users with regard to age, sex, concomitant drug use, and prevalent comorbidities at the time of their first pioglitazone prescription, specifically hypertension and ischemic heart disease. As pioglitazone is indicated in combination therapy with other oral antidiabetics like metformin, sulfonylurea, and insulin, the concomitant use of other oral antidiabetics as well as use of insulin in pioglitazone users will also be described. The study will describe patients who have commenced treatment with pioglitazone, whether added to previous therapy, or as a switch to pioglitazone from other oral antidiabetic medication. The key demographics will be presented before and after each major change to the product information (removal of contraindication and inclusion of indication for use with insulin January 2007; contraindication on use in patients with bladder cancer July 2011) or other factors potentially affecting pioglitazone use (suspension of rosiglitazone from the EU market in September 2010), to examine whether there are temporal trends.

Pioglitazone can cause fluid retention, which may exacerbate or precipitate heart failure. There have been cases of cardiac failure reported when pioglitazone was used in patients having a history of cardiac failure, and the risk of cardiac failure may be higher in patients coprescribed pioglitazone and insulin. The incidence of heart failure will be stratified according to whether or not insulin is coprescribed.

With regards to the assessment of the risk minimization measures, the diabetic patients who receive pioglitazone despite the contraindications will be described, and classified according to which contraindication(s) apply.

This study will be conducted in 2 separate databases and report consequently 2 sets of results, which will be compared and contrasted in 1 integrated discussion.

2.0   BACKGROUND

The thiazolidinedione pioglitazone, is a peroxisome proliferator-activated receptor agonist that affects regulators of carbohydrate and lipid metabolism. Pioglitazone reduces insulin resistance by enhancing the action of insulin, thereby promoting glucose utilization in peripheral tissues, suppressing gluconeogenesis, and reducing lipolysis and may provide an alternative first-line treatment for type 2 diabetes [1]. Pioglitazone is used for the treatment of type 2 diabetes along with a healthy diabetic diet, regular exercise, weight control, smoking reduction, and careful monitoring of blood glucose. Pioglitazone is indicated as monotherapy or in combination with metformin or sulfonylureas which are medications in different classes of antidiabetic drugs that also lower blood glucose. Since it requires naturally-secreted insulin to be effective, pioglitazone is not recommended in type 1 diabetes where the amount of insulin is very low or absent.

Before 2007, in Europe, pioglitazone was contraindicated for use in combination with insulin. On 31 August 2007 pioglitazone was approved in Europe for use in combination with insulin in type 2 diabetes mellitus patients with insufficient glycemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance. Of note: in the United States and Switzerland, this indication has been approved since the first marketing approval in 1999.

In 2011 the European Commission initiated the Article 20 procedure for pioglitazone containing products and requested the European Medicines Agency (EMA) to review the benefits and risks in association with bladder cancer. The conclusion of this procedure in July 2011 resulted in some new risk minimization measures for pioglitazone (see below).

2.1   Heart Failure

The background incidence rate of congestive heart failure in diabetic patients is estimated to be 309 per 10,000 patient-years [2].

In pioglitazone clinical trials, cardiac failure is frequently reported as a nonserious adverse event and the fact that pioglitazone causes peripheral edema may impact on the accuracy of the diagnostic differentiation between simple peripheral edema and edema as part of the symptoms for heart failure. In the high-risk diabetic population of the PROspective pioglitAzone Trial in macroVascular Events (PROactive) outcome study, more cardiac failure events were reported with pioglitazone than with placebo; however, outcomes were not worsened for these patients and no increase in mortality resulted [3,4].

2.2   Bladder Cancer

On 18 March 2011, the European Commission initiated the Article 20 procedure for pioglitazone containing products and requested the EMA to review the benefits and risks in association with bladder cancer.

In July 2011, at the Committee for Medicinal Products for Human Use meeting, bladder cancer was added to the risk management plan as an identified risk and the following wording was incorporated into the EU SmPC:

Contraindications

Pioglitazone is contraindicated in patients with:

- *current bladder cancer or a history of bladder cancer*

- *uninvestigated macroscopic haematuria*

Special warnings and precautions for use

Bladder Cancer

Cases of bladder cancer were reported more frequently in a meta-analysis of controlled clinical trials with pioglitazone (19 cases from 12506 patients, 0.15%) than in control groups (7 cases from 10212 patients, 0.07%) HR=2.64 (95% CI 1.11-6.31, P=0.029). After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 7 cases (0.06%) on pioglitazone and 2 cases (0.02%) in control groups. Available epidemiological data also suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone in particular in patients treated for the longest durations and with the highest cumulative doses. A possible risk after short term treatment cannot be excluded.

Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment (risks include age, smoking history, exposure to some occupational or chemotherapy agents e.g. cyclophosphamide or prior radiation treatment in the pelvic region). Any macroscopic haematuria should be investigated before starting pioglitazone therapy.

Patients should be advised to promptly seek the attention of their physician if macroscopic haematuria or other symptoms such as dysuria or urinary urgency develop during treatment.

2.3   Assessment of Benefit of Therapy

In addition, as part of the Article 20 procedure, the following wording was introduced into section 4.1 of the SmPC:

After initiation of therapy with pioglitazone, patients should be reviewed after 3 to 6 months to assess adequacy of response to treatment (e.g. reduction in HbA1c). In patients who fail to show an adequate response, pioglitazone should be discontinued. In light of potential risks with prolonged therapy, prescribers should confirm at subsequent routine reviews that the benefit of pioglitazone is maintained (see section 4.4).

It is proposed that the implementation of this in clinical practice should be assessed by this study.

3.0   OBJECTIVES

1. To describe the utilization patterns of pioglitazone for the period up to 31 August 2007, between 31 August 2007 and September 2010, between September 2010 and July 2011 and after July 2011.

2. To estimate the incidence and prevalence of heart failure in diabetic patients prescribed pioglitazone, both overall and stratified by insulin comedication status.

3. To describe the patients who were given pioglitazone despite of the contraindications given on its label. This analysis will be conducted prior to and post July 2011.

    a) Prior to July 2011 the contraindications will comprise cardiac failure or history of cardiac failure (New York Heart Association stages 1 to 4), hypersensitivity to the active substance or to any of the excipients.

    b) Post July 2011 the contraindications will additionally include history of, or current, bladder cancer. The analysis of data after the introduction of bladder cancer risk minimization measures will also describe adherence to the new contraindication in patients who were prevalent pioglitazone users.

4. To describe the frequency of monitoring of factors used in the assessment of effectiveness of treatment prior to and after July 2011.

4.0   METHODS

4.1   Data Source

PHARMO databases

A prior drug utilization study performed by PHARMO for Takeda used pharmacy data as well as hospital admission data. A limitation of the combination of these databases is that heart failure could not be determined very reliably, since not all patients that are hospitalized for heart failure. To develop a prediction model for heart failure based on drug use GP records were used, resulting in an algorithm to predict the number of heart failure cases in the combined pharmacy and hospital dataset based on drug use. At that time the GP dataset was considered too small (500,000 patients) to determine pioglitazone utlization patterns.

For the current study PHARMO will be using the GP dataset, despite lower numbers in pioglitazone users compared to the linked pharmacy and hospital admission records.

1. The specificity and sensitivity of the algorithm predicting the probability of heart failure based on drug use was rather low. The GP database contains actual diagnoses, both as ICPC codes and in free journal text.

2. Detection of bladder cancer would be incomplete using hospital admission data, since not all patients with bladder cancer will undergo surgery and thus require hospitalization. ICPC codes and free text can be used in the GP journals.

3. Symptoms such as macroscopic haematuria cannot be determined in pharmacy and hospital data, but are available both as ICPC and free text in GP journals.

The PHARMO GP database is updated annually in January/February then remains static for the following 12 months. The database currently covers up to January 2012.

PHARMO is continually expanding the GP database population. The current GP database contains 1.1 million patients, and 2300 pioglitazone users with more than one pioglitazone prescription. A further expansion of the database by approximately 30% was undertaken in April 2012 (with data coverage up to January 2012). This would likely expand the number of eligible pioglitazone users to around 3000.

General practitioner database (PHARMO database for which general practitioner permission is needed)

The general practitioner database is a longitudinal observational database that contains data from computer-based patient records of general practitioners (GPs) throughout the Netherlands, who voluntarily chose to supply data to the database. GPs receive completely control usage of their data, through the Steering Committee and are permitted to withdraw data for specific studies. Collaborating practices are located throughout the Netherlands and the collaborating GPs are comparable to other GPs in the country based on age and gender.

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The general practitioner database currently includes about 1.5 million patients. This is the cumulative amount of patients who have ever been part of the dynamic cohort of patients who were registered. Turnover occurs as patients move and transfer to new practices. The records of 'transferred out' patients remain in the database and are available for retrospective studies with the appropriate time periods.

Detailed clinical information and prescription drugs data are captured in this database, including among others demographic data (age, sex, patient identification, GP registration information), diagnoses, physician-linked indications for therapy, comorbidity, drug prescriptions, laboratory values (eg, potassium, creatinine), doctor in attendance, referrals to specialists, and a 'medical chart' containing free-text as noted by the general practitioner. Diagnoses and symptoms are recorded based on the International Classification of Primary Care (ICPC), which can be mapped to ICD-9 codes, but diagnoses and complaints can also be entered as free text [5]. Prescription data such as product name, quantity dispensed, dosage regimens, strength, and indication are entered into the computer. Prescriptions include medications prescribed by the GP (please note that specialist prescriptions are generally not included in the GP data). The National Database of drugs, maintained by the Royal Dutch Association for the Advancement of Pharmacy, enables the coding of prescriptions, according to the Anatomical Therapeutic Chemical classification scheme recommended by the World Health Organization. The system complies with European Union guidelines on the use of medical data for medical research and has been validated for pharmaco-epidemiological research [6]. Approval for this study will be obtained from the "Raad van Toezicht" an ethical review board. For confidentiality reasons, the database is strictly anonymized.

4.2   Study Population

We will identify all diabetic patients in the PHARMO database who ever received ≥1 prescription for pioglitazone, alone or in a combination therapy with metformin, a sulfonylurea drug, other oral antidiabetic drugs, or insulin, between June 1999 and May 2012 for the analysis relating to objectives 1 and 2 (heart failure and comedication with insulin). This will also form the interim analysis dataset for the assessment of the performance of risk minimization measures and periodic review of benefit (objectives 3 and 4). Date of first pioglitazone will be defined as cohort entry date (CED). Patients will be included in the study if they have at least one year registration in the PHARMO database before CED. The Observational research file (ORF) will include all information between a year before start CED until end of follow.up.

4.3   Data Analysis

Characterization of the study population

All patients who ever received ≥1 prescription for pioglitazone and have at least one year registration in the PHARMO database before first prescription of pioglitazone (CED) will be included in the analyses. Characterization of the study population at baseline will include

- age at first pioglitazone use

- gender

- body mass index (BMI, most recent assessment prior to pioglitazone use)

- smoking status (most recent assessment prior to pioglitazone use)

- frequency of HbA1c, glucose, lipid profile, creatinine and BMI assessments

- the calendar year in which the pioglitazone treatment was started

- duration of diabetes (prevalent/incident). Prevalent diabetics will have a history of ≤6 months between start ORF and the earliest of first recorded type 2 diabetes diagnosis or of use of other antidiabetic drugs. Incident diabetics will have a history of ≥6 months between start ORF and the earliest of first recorded type 2 diabetes diagnosis or of use of other antidiabetic drugs

In the year before cohort entry date

- prior drug use (diabetes medication, cardiac medication (nitrates, digoxin) antihypertensive drugs, spironolactone, loop diuretics, antibiotics used in urinary tract infections)

- prior morbidity (hypertension, heart failure, ischaemic heart disease (i.e. a history of angina pectoris or myocardial infarction), cardiac failure, peripheral vascular disease, cerebrovascular disease, macroscopic haematuria (uninvestigated or investigated (i.e. followed by mention of menstrual cycle, diagnosis of / treatment for urinary tract infections, bladder cancer or other urinary diagnoses, or referral to urologist), renal disease, chronic renal disease (including dialysis), and or obstructive pulmonary disease (COPD).

These will be assessed by retrospectively examining the date stamped entries in the GP records, looking for symptoms and diagnoses (ICPC coded or free text), prescriptions, as well as risk factors and disease indicators that are periodically recorded as part of the diabetes monitoring program implemented in primary care in the Netherlands (e.g. smoking status, BMI, diabetes duration). ICPC codes may be provided in a problem list (chronic health issues), episode list (limited to a specific time frame) or with a prescription. Since heart failure is usually considered to be a chronic condition, and it will be impossible to determine reliably from the database whether heart failure is a temporary condition, patients with a diagnosis of heart failure

anywhere in their recorded history will be considered prevalent heart failure patients at the start of pioglitazone use.

Exact ATC and ICPC codes to be used in the analysis will be provided in the analysis plan.

Reporting of the characteristics will be done per sub-cohort based on stratifications necessary in each analysis. The key demographics will be presented before and after each major change to the product information or other factors potentially affecting pioglitazone use (31 August 2007, September 2010, July 2011).

The methods used in the analyses are described below per objective.

1. To describe the utilization patterns of pioglitazone for the period up to 31 August 2007, between 31 August 2007 and September 2010, between September 2010 and July 2011and after July 2011.

Concomitant insulin and other antidiabetic drug use will be assessed after start of first pioglitazone to learn more about drug utilization patterns of patients who are newly started on pioglitazone. At the start of pioglitazone use it will be assessed whether patients received pioglitazone as monotherapy, or in addition to other oral antidiabetic drugs/insulin. It will be assessed with which oral antidiabetic drugs pioglitazone is usually combined, what proportion of patients gets a new pioglitazone treatment to replace a previously used oral antidiabetic drug such as metformin (proportions of first/second line treatment), and how many pioglitazone users also use insulin. The proportions of these patterns at start of therapy will be described for patients starting pioglitazone use in the period up to 31 August 2007, between 31 August 2007 and September 2010, between after September 2010 and July 2011 and after July 2011.

The pioglitazone treatment duration (mean and standard deviation, median and interquartile range) will be determined over the entire study period up to the end of available GP records. Individual pioglitazone treatment duration will be independent of changes in concomitant glucose lowering drugs. The duration will be determined based on the prescribed number of tablets and daily dose of all pioglitazone prescriptions. Prescriptions predating the end of the previous prescription will be assumed to start after the end of the previous prescription (start date will be shifted for the calculation of the total duration of treatment).

Where there is no information available from number of tablets, prescription duration or number of tablets per day

- if the interval between prescriptions is greater than 3 months, the prescription duration will be assumed to be 3 months (i.e. the maximal legal duration for a drug dispensing in the pharmacy).

- in the absence of another prescription, the prescription duration will be assumed to be the median of the durations of the prior prescriptions.

In the event that a patient leaves the database, exposure will be assumed to cease.

2. To estimate the incidence and prevalence of heart failure in diabetic patients prescribed pioglitazone, both overall and stratified by insulin comedication status.

The overall analysis will be performed using data from the entire study period, the stratified analysis will use data up to a change in concomitant insulin treatment: patients will be stratified based on index use of concomitant insulin use and will no longer be followed after a change in insulin treatment. We will assess for all new pioglitazone users whether they had at the time of the first prescription a prevalent diagnosis of hypertension, ischemic heart disease (ie, a history of angina pectoris or myocardial infarction), or cardiac failure. Those with cardiac failure at the start of treatment will not be included in the incidence rates. We will further identify all new cases of cardiac failure after the start of pioglitazone therapy, overall and stratified by insulin comedication status. We will assess person-time from the time of the first pioglitazone prescription until the recording of an incident diagnosis of heart failure (excluding patients with prevalent heart failure, which in this study will be considered irreversible) and calculate incidence rates, stratified by the presence of insulin comedication, age, and sex.

3. To describe the patients who were given pioglitazone despite of the contraindications given on its label. This analysis will be conducted prior to and post July 2011.

Prior to July 2011 the contraindications will comprise

- cardiac failure or history of cardiac failure

- hypersensitivity to the active substance or to any of the excipients is highly unlikely to be recorded, and neither is a clinician likely to prescribe pioglitazone to a patient with previous known hypersensitivity to pioglitazone. However, the journals will be searched for any such information and when this analysis does seem possible it will be reported.

At the initiation of pioglitazone use prior to July 2011 patient characteristics including drug utilization (see objective 1) will be shown stratified by prevalent cardiac failure, and if possible hypersensitivity to the active substance or to any of the excipients. The proportion of patients with prevalent bladder cancer at the time of initiation will also be shown as part of the characteristics.

After July 2011 the contraindications will comprise

- cardiac failure,

- bladder cancer

- uninvestigated haematuria

- if possible hypersensitivity to the active substance or to any of the excipients (see comments above)

For the study period after July 2011, prevalent pioglitazone users and newly initiated pioglitazone users will be reported separately, and patient characteristics will be stratified based

on contraindications (cardiac failure, or bladder cancer or uninvestigated haematuria). For prevalent cases of bladder cancer and uninvestigated haematuria it will be assessed whether pioglitazone treatment was stopped at the time of the label change. For incident cases it will be assessed whether pioglitazone treatment was stopped at the time of the diagnosis of bladder cancer or symptoms of macroscopic haematuria.

4. To describe the monitoring of factors used in the assessment of effectiveness of treatment prior to and after July 2011.

In order to assess the adherence to the effectiveness measures, we will determine whether the frequency of HbA1c and glucose follow-up measurements is in line with the label change of July 2011. The frequencies of assessments of HbA1c, glucose, lipid profiles, plansma creaetine concentrations, BMI and any other measurements /parameters that may be taken into account by clinicians to evaluate effectiveness of treatment will be reported. The frequencies will be reported separately for the periods up to September 2010, September 2010-July 2011, and after July 2011, to see whether the frequencies changed, possibly due to the label changes.

Also, the number of patients stopping pioglitazone treatment within one week of an HbA1c or glucose measurement will be assessed.

Impact of Age on risks

Although older age is not a contraindication of pioglitazone, as most of the health risks associated with use of pioglitazone are also heavily dependent on age, all relevant tables/figures will be stratified by age in the following categories: $<65, \geq 65$.

The statistical software SAS (release 9.2, SAS Institute, Inc., Cary, NC, USA) will be used to conduct the analyses.

Cross-tabulations of the various parameters of interest will be provided to tabulate proportions in different subcohorts based on (possible) contraindications. Various regulatory actions were taken with respect to rosiglitazone and pioglitazone after 2006 and so we will compare comorbidities and contraindications among new users of pioglitazone before and after each of these various time points.

Study timelines

It is proposed that the study will report at 2 time points.

*   The final report for objectives 1, 2, and 3a will be submitted in October 2012 together with an interim report on objectives 3b and 4, and will included data collection up to January 2012.

- The final report on objectives 3b and 4 will be submitted in March 2013 and will include data collection up to January 2012. It is noted that no additional new data will be available between the interim and final reports.

5.0   LIMITATIONS

It is possible that we will miss certain diagnoses when searching for a history of comorbidities at the time of the first pioglitazone prescription if a disease has not yet been detected, or has not been appropriately recorded by the GP. We cannot rule out that the prevalence of certain comorbidities may be slightly underestimated for the reason stated above.

The categorization of haematuria as uninvestigated has to be deduced from further diagnoses or referrals. Recording of these referrals or diagnoses may be incomplete, leading to an overestimation of uninvestigated haematuria.

Another limitation is that the GP data record diagnoses in free text, or as ICPC codes in a problem list for chronic problems, and episode list for transient problems, or as indication with a prescription. The GP journal does not mandate that ICPC codes be given, and the coding is therefore unreliable and its accuracy with regard to chronic and transient diagnoses cannot be determined. This has implications for the determination of heart failure: since heart failure is usually a chronic condition, any occurrence of the diagnosis in the history of the patient will automatically be considered to indicate a chronic problem. It will therefore not be possible to stratify incidence rates of heart failure based on heart failure in the patients history: patients with a history are considered prevalent cases and are excluded from incidence rates calculations.

Also, we cannot rule out that the start of therapy is initiated by a specialist, and that the first prescriptions by the specialist are not recorded in the GP data.

6.0   REFERENCES

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7.0   APPENDICES

Code Lists

Cardiovascular Conditions ICPC

K77   heart failure
K76   ischaemic heart disease without angina (includes cardiomyopathy among other things)
K82   Pulmonary heart disease
K83   Heart valve disease NOS
K84   Heart disease other

Hepatic impairment ICPC

D97   Liver disease NOS

Urinary tract conditions ICPC

U6   haematuria
U76   Malignant neoplasm of bladder

ATC Codes

Thiazolidinediones

- A10BG thiazolidinediones
  A10BG02 Rosiglitazone (Avandia)
  A10BG03 Pioglitazone (Actos)

- A10BD Combinations of oral blood glucose lowering drugs
  A10BD03 rosiglitazone and metformin
  A10BD04 rosiglitazone and glimepiride
  A10BD05 Pioglitazone and metformin
  A10BD06 Pioglitazone and glimepiride
  A10BD09 Pioglitazone and alogliptin

Insulin and analogues

- A10A Insulin and analogues
- Other oral antidiabeticsA10BA Biguanides metformin
  A10BA02 metformin
- A10BB Sulfonamides, urea derivatives
- A10BC Sulfonamides (heterocyclic)
- A10BD Combinations of oral blood glucose lowering drugs
- A10BF Alpha glucosidase inhibitors
- A10BH Dipeptidyl peptidase 4 (DPP-4) inhibitors
- A10BX Other blood glucose lowering drugs, excl. insulins