Executive summary

This descriptive drug utilization study (DUS) aimed to assess the effectiveness of the risk minimization measures for pioglitazone, which were implemented on 21 July 2011 within the UK (study period: from 21 July 2011 to 31 December 2013). This DUS focused on first-line use of pioglitazone within the UK, the risk of incident heart failure (HF) during pioglitazone therapy (with and without insulin comedication), prescription behavior in case of incident bladder cancer (BC) or uninvestigated macroscopic hematuria during pioglitazone treatment, as well as on the impact of HbA1c monitoring values on the prescription patterns of pioglitazone after the label change in July 2011. Results were compared to the 2012 DUS, which assessed pioglitazone prescription patterns between June 1999 and June 2012.

We identified 1808 new users of pioglitazone (study population 1 [SP1]), as well as 12,986 prevalent pioglitazone users (study population 2 [SP2]) after 21 July 2011. Overall, patients within SP1 were comparable to the 2012 DUS study population in terms of age, prevalent comorbidities (hypertension 56.8%, hyperlipidemia 30.5%), and Type 2 Diabetes Mellitus (T2DM) disease stage at the time of treatment initiation. However, less patients within SP1 (5.4%) received pioglitazone as a first-line antidiabetic treatment, as compared to the 2012 study population (13.3%), which may indicate better compliance with the prescribing information of pioglitazone after 21 July 2011, a drug that is only indicated as first-line treatment in patients in whom the use of metformin is inappropriate.

Results regarding incident HF are not comparable between this DUS and the one from 2012, as we calculated cumulative incidence rates (CIRs) in the herewith presented study (person-year based incidence rates were used in the 2012 DUS), and inclusion criteria for HF cases differed between the two studies. Sample size was small in SP1, which limited the interpretation of results. We observed an overall CIR of 0.52% (67 HF patients) between 21

July 2011 and December 2013 within SP2 (higher in men, and increasing with increasing age). The highest CIR of 1.00% was observed in the subgroup of pioglitazone users with concomitant insulin use during this time period, whereas patients with prevalent pioglitazone without insulin use had a CIR of 0.46%. Patients with prevalent insulin use without pioglitazone use had a CIR of 0.70%, which was also slightly higher in men than in women and in older age-groups. Overall, there is no strong evidence for multiplicative interaction between pioglitazone and insulin on the risk of incident HF. An additive effect of pioglitazone and insulin on the risk of developing HF may be present, but results have to be interpreted cautiously due to potential residual confounding and due to small sample size. Furthermore, use of an increasing number of antidiabetic drug classes may be a proxy for advanced T2DM disease stage, which itself is a risk factor for the development of HF.[11]

Overall, absolute risks for incident BC in pioglitazone users after 21 July 2011 were low (CIR 0.11% in SP1 and CIR 0.22% in SP2). Sample size in SP1 was small due to short follow-up time, which limited the interpretation of the findings. In SP2, relatively more patients (44.0%) had their pioglitazone treatment stopped immediately after an incident BC diagnostic record, as compared to the 2012 DUS (37.5%), which may indicate a trend of increasing awareness to potential adverse events of pioglitazone.

Of all patients with incident macroscopic hematuria during pioglitazone treatment after 21 July 2011, 1 out of 13 (7.7%) patients in SP1 and 7 out of 138 (5.1%) in SP2 had uninvestigated hematuria, whereas all other patients were followed-up by a referral to a urologist and / or a microbiologic urine assessment with or without subsequent antibiotic treatment within 90 days following the diagnostic record.

Although incidence density rates (IDRs) of therapy monitoring for glucose, creatinine, blood lipids, and BMI complied with UK national guidelines (NICE guidelines for the treatment

of T2DM within the UK[1]), less than 6% of patients with a recorded HbA1c value >7.5% after 21 July 2011 stopped therapy thereafter in SP1 and SP2, whereas the majority of patients (>60%) had ≥3 prescriptions recorded thereafter. This observation did not change when we set the HbA1c cut-off at 9%. Overall, slightly more patients had an ongoing pioglitazone therapy recorded after a high HbA1c value, as compared to the 2012 DUS (approx. 50% with an ongoing therapy of ≥3 prescriptions), but this discrepancy may be attributable to the longer follow-up time after 21 July 2011 in the present study. Although patients were overall slightly more likely to stop pioglitazone therapy in case of HbA1c value deterioration during pioglitazone therapy, the overall impact of HbA1c monitoring on pioglitazone treatment decisions was marginal. However, decisions on treatment discontinuation / continuation with pioglitazone are multifactorial, with various clinical aspects playing a role besides therapy effectiveness, such as tolerability, individual patient preferences, or changes in the regimen of other concomitantly prescribed drugs. These aspects were not assessed in the present DUS.

Taken together, the results of this study provide assurance, that the label changes implemented in July 2011 are appropriate with respect to patient safety.