Executive summary

Objective

Since the introduction of pioglitazone to the European Union a number of changes to the Summary of Product Characteristics (SmPC) have occurred and Rosiglitazone was suspended from the European market in September 2010. This observational study is an evaluation of the impact of these changes on the prescription patterns of pioglitazone and on the implementation of risk minimization measures introduced in July 2011 regarding bladder cancer and heart failure, based on monitoring of treatment benefits and contraindications.

Methods

Pioglitazone users were identified in the Dutch PHARMO GP database of 1.5 million patients. The study included all pioglitazone users with a history of medical records of at least 1 year prior to the start of pioglitazone.

Contra-indications, patterns of pioglitazone use and monitoring frequencies were investigated relative to milestone dates relating to label changes and the suspension of rosiglitazone.

Results

Of the 2,238 pioglitazone users included from 2003 onwards, 30% started after 2007. 50% were male, and 56% were aged under 65. In the year before start of pioglitazone, 67% were treated for hypertension, 3% had a diagnosis of ischaemic heart disease (IHD), and <0.5% had a recorded diagnosis of heart failure (HF), although 2% used spironolactone, and 9% used loop diuretics, medications often used to treat HF.

Contraindications

During treatment the incidence of HF was 0.84 per 100 person years (95% CI 0.62-1.12), 0.80 (0.58-1.08) among those without insulin use, and 1.46 (0.47-3.41) with insulin use. Incidence rates were 6 times higher among elderly patients (16.4 (95% CI 11.6-22.5)) than among patients aged under 65 (2.7 (95% CI 1.3-5.2)). As only 47 cases of heart failure were recorded during treatment, all patients starting pioglitazone use before September 2010, it was not possible to evaluate changes in incidence rates over time.

Hypersensitivity for pioglitazone or its excipients, including recorded adverse events, was found in 10 patients, 3 of which stopped using pioglitazone.

There was only 1 case of bladder cancer in the year prior to start of pioglitazone use, 6 in the entire available history. 7 (0.3%) cases were identified during treatment. One case with a diagnosis 7 years prior to starting pioglitazone, and one case identified during treatment continued pioglitazone use after the bladder cancer warning was added to the SmPC.

None of the 3 patients (0.1%) with uninvestigated haematuria in the year before start of pioglitazone had a repeat diagnosis after starting therapy. Of the 7 (<0.3%) newly diagnosed uninvestigated haematuria cases before the SmPC change in 2011, 6 continued use after the

SmPC change, but none had a repeat diagnosis of haematuria. There were no new cases of uninvestigated haematuria after July 31st 2011.

Utilization

In accordance with the label, pioglitazone was prescribed mainly as second line therapy (95%), mostly as add on to prior treatment. Among those receiving pioglitazone as first line therapy (5% of all users), 83% were treated with pioglitazone only. Overall, pioglitazone was initiated as monotherapy in 17% of users. The percentage of insulin users was relatively stable over time, also during follow-up. Only 7% switched from rosiglitazone, of which only one third after withdrawal of rosiglitazone.

Monitoring

Monitoring of treatment effectiveness and risk increased slightly over time. Since diabetes monitoring programs were implemented in the Dutch healthcare system since 2000, frequencies of monitoring were quite high during the entire study period, and only a slight increase in the monitoring of HbA1c, glucose, lipids, creatinine and BMI was observed since the first SmPC change in 2007. No further changes were observed since then.

Conclusion

In this study, limited contraindications were found with the use of pioglitazone, with regards to heart failure, bladder cancer or hypersensitivity. However, the increased risk of heart failure associated with concomitant insulin use may deserve extra attention. Monitoring of HbA1c, glucose, and/or lipid was performed in a relatively high proportion of patients. This high frequency of monitoring can be attributed to the fact that diabetes monitoring programs are used as a standard clinical practice in diabetes mellitus patients in the Netherlands. Therefore, only a slightly increase in monitoring was observed after monitoring recommendation being added to the SmPC.