Impact of risk minimisation in patients treated with rosiglitazone-containing products
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Executive Summary

Rosiglitazone is an insulin sensitizer, indicated for treatment of type 2 diabetes mellitus in adults. Rosiglitazone-containing products have been marketed in the European Union (EU) since 2000; later also combined with metformin and with glimepiride. Rosiglitazone has been subject to multiple benefit-to-risk assessments, especially in relation to cardiovascular safety. After several amendments to the product label, and after publication of studies suggesting increased risk of cardiovascular outcomes, the European Medicines Agency (EMA) recommended suspension of all rosiglitazone-containing products from the EU markets, on 23 September 2010. Following its decision, EMA commissioned the present study to examine population-level changes in utilization of rosiglitazone containing products and patient-level effects on glycaemic control and other objective parameters of disease in response to initiation or termination of such products.

This study was conducted in population-based samples from Denmark and the United Kingdom (UK). Data linked from population health registries of two northern regions, representing about 33% of the population, were used in Denmark; data from the General Practice Research Database (GPRD), representing about 6% of the population, were used in the UK. The study population was defined as users of oral hypoglycaemic agents (OHA) in 2000-2010. Utilization dynamics, proportion of users with contraindications, and prevalence of off-label use of rosiglitazone-containing products were traced over time, in particular in relation to EMA regulatory actions and scientific publications relevant to risk assessment. On the patient level, changes in glycaemic control (glycated haemoglobin, fasting plasma glucose), biochemical parameters of kidney and liver functions, and acute events following initiation and termination of rosiglitazone-containing products were examined.

During the study period, there were 2,321 initiators of rosiglitazone-containing products in Denmark and 25,428 initiators in the UK. Over the marketing life of rosiglitazone, proportion of rosiglitazone-product users among all OHA users peaked at 4% in Denmark and at 15% in the United Kingdom. Both peaks occurred in May 2007. Following publication of the meta-analysis by Nissen and Wolski, in May 2007, showing evidence of increased cardiovascular morbidity and mortality, the proportions of rosiglitazone-product users among all OHA users declined in both countries. In northern Denmark, proportion of rosiglitazone users with a history of a cardiac contraindication (ascertained by hospital visits), recorded in the 12 months before the first rosiglitazone prescription ranged between 6% and 9%. In the United Kingdom, proportion of rosiglitazone users with a history of cardiac contraindications recorded since 1987 decreased over time from nearly 25% to close to 14%.

Before initiation of rosiglitazone-containing products, mean glycated haemoglobin (HbA1c) was 8.5% among patients in northern Denmark and 8.9%, in the UK, and decreased over 12 months post-initiation, on average by 1.0% in both countries. More than half of patients with available measurements had a decrease in HbA1c of 0.6% or more after initiating rosiglitazone. Loss of glycaemic control, defined by new onset of HbA1c >7.5%, was registered for up to 16% of patients during the follow-up in Denmark and for 21% of the patients in the United Kingdom. The 45-day risk of death from all causes after initiation of rosiglitazone-containing products was 0.22% (95% CI: 0.03-0.40) in northern Denmark and 0.13 (95% CI: 0.09-0.18) in the United Kingdom.

Before termination of rosiglitazone-containing products, mean HbA1c ranged from 8.3% to 8.5% in Denmark and from 8.3% to 8.4% in the UK. At 12-months post-termination, HbA1c had a mean decrease of 0.63% in Denmark and a mean decrease of 0.17% in United Kingdom. Less than half of persons with measurements had a decrease of more than 0.6% in HbA1 after EMA/2010/38/CN Risk minimisation and rosiglitazone-containing products termination of rosiglitazone. Loss of glycaemic control, defined by new occurrence of HbA1c >7.5%, was registered for up to 29% of patients during the follow-up in Denmark and for up to 37% of the patients in the United Kingdom. The 45-day risk of death from all causes after termination of rosiglitazone-containing products was 1.31% (95% CI: 0.82-1.81) in Denmark and 0.30 (95% CI: 0.24-0.38) in the United Kingdom.

This investigation showed that adjustment of labelling in response to the meta-analysis with evidence for increased cardiovascular morbidity was associated with a decline in utilization of rosiglitazone-containing products. Changes in objective parameters of disease or acute events observable from the data at hand did not differ substantially after initiation or termination of rosiglitazone-containing products.