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Mrs Sarah Morgan  
Dr Julie Beynon  
Dr Jane Woolley  
Dr Rafe Suvarna  
Dr June Raine

Medicines and Healthcare Products Regulatory Agency  
51 Buckingham Palace Road  
Victoria  
London, SW1W 9SZ

Dear All,

Re Pioglitazone and bladder cancer

We understand that EMA is shortly to have its routine review concerning the safety of pioglitazone with regard to risk of bladder cancer.

ABCD is the national association of diabetes consultant specialists in the UK.

ABCD deems patient safety to be of paramount importance and we applaud close scrutiny of all data by professionals equipped with the appropriate skills to interpret it.

Nevertheless ABCD is extremely concerned that France and Germany have suspended new prescriptions of pioglitazone in advance of the EMA meeting.

Type 2 diabetes is more than anything a disease of people dying prematurely of cardiovascular disease. Pioglitazone is the only glycaemic medication other than metformin with randomised controlled trial evidence that it reduces death, myocardial infarction and stroke (1). If it is suspended prematurely we may be losing an agent with such benefit for the sake of as yet uncertain, unproven risk.

Pioglitazone is particularly beneficial in reducing the chances of a patient who has had a stroke from having further stroke (Figure 1) (2).
Figure 1: Kaplan-Meier curve of the time to fatal/nonfatal stroke in the patients in PROactive who had had a previous stroke. The solid line represents the pioglitazone group; the dashed line represents the placebo group. CI = confidence interval; HR = hazard ratio. Also published in Wilcox R, et al, Stroke 2007; 38: 865–873.

Similarly pioglitazone reduces the chances of a patient who has had a myocardial infarction or acute coronary syndrome from having a repeat event (Figure 2) (3).

Figure 2: Kaplan-Meier curve of the time to fatal/nonfatal myocardial infarction (MI) (excluding silent MI) in patients in PROactive who had had a previous myocardial infarction. The solid line represents the pioglitazone group; the dashed line represents the placebo group. CI = confidence interval; HR = hazard ratio. Also published in Erdmann E, et al, J Am Coll Cardiol 2007; 49: 1772–1780
Whilst a meta-analysis of rosiglitazone trials raised the possibility of cardiovascular harm associated rosiglitazone (4), a similar meta-analysis of pioglitazone trials showed that among a diverse population of patients with type 2 diabetes, pioglitazone treatment was associated with a significantly lower risk of death, myocardial infarction or stroke (5).

A retrospective cohort study using the UK general practice research database (91521 patients with diabetes) suggested that pioglitazone was associated the lowest all cause mortality amongst the oral hypoglycaemic agents (6).

Randomised controlled trials of markers of carotid and coronary atherosclerosis (carotid intima-media thickness and intravascular ultrasound) have shown benefit for pioglitazone compared to sulphonylureas (7,8).

The primary composite endpoint in the PROactive study did not achieve statistical significance. Nevertheless, as shown by table 1 below, taken from that study, the first six factors in the primary composite endpoint: death, non fatal myocardial infarction, silent myocardial infarction, stroke, major leg amputation and acute coronary syndrome do show significant benefit for pioglitazone. Statistical significance is lost only when coronary and leg revascularization are added. It has been suggested that this outcome might be explained by pioglitazone preserving people from death, myocardial infarction, acute coronary syndrome and leg amputation to be available for coronary or leg revascularisation (9,10). This interpretation suggests a real benefit of pioglitazone in the treatment of Type 2 diabetes.

<table>
<thead>
<tr>
<th>Primary composite endpoint</th>
<th>Main secondary endpoint</th>
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<tbody>
<tr>
<td>Pioglitazone (n=2605)</td>
<td>Placebo (n=2633)</td>
</tr>
<tr>
<td>Placebo (n=2633)</td>
<td>Pioglitazone (n=2605)</td>
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<td></td>
<td>Placebo (n=2633)</td>
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<tr>
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<td>514</td>
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<tr>
<td>Non-fatal MI (excluding silent MI)</td>
<td>85</td>
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<tr>
<td>Silent MI</td>
<td>20</td>
</tr>
<tr>
<td>Stroke</td>
<td>76</td>
</tr>
<tr>
<td>Major leg amputation</td>
<td>9</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>42</td>
</tr>
<tr>
<td>Coronary revascularisation</td>
<td>101</td>
</tr>
<tr>
<td>Leg revascularisation</td>
<td>71</td>
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</tbody>
</table>

Table 1: Numbers of first events contributing to the primary composite and main secondary endpoints in the PROactive study. From Dormandy JA, et al, Lancet 2005; 366: 1279–1289.

Pioglitazone is widely prescribed in the UK and there are many patients who are stable with good glycaemic control on this agent. We believe that pioglitazone is making a major contribution to the improvement in glycaemic control amongst our patients – and it is accepted that improved glycaemic control is associated with improved microvascular outcomes (11,12).
It has been suggested that metformin, pioglitazone and GLP1 agonists may represent the optimum combination of agents for the modern management of type 2 diabetes based on the pathophysiology of the disease (13, 14).

If pioglitazone use is suspended many patients will experience worsening of glycaemic control and risk from acute hyperglycaemic syndromes as well as potentially increased microvascular and macrovascular damage.

Pioglitazone will shortly emerge from patent and with the exception of sulphonylureas there are no other popular alternative low cost pharmaceutical options.

A substantial number of people with diabetes are on triple oral hypoglycaemic therapy including pioglitazone so in the event of total withdrawal many will need to change to expensive options including injectables (a major stress on specialist resources nationally) or gliptins. A number of occupational drivers may lose their licence as a result of a total withdrawal of pioglitazone—these include occupational drivers on pioglitazone alongside GLP1-based treatment most of whom will migrate to insulin or be inadequately controlled.

Gliptins have an increasing market share and are a pressure on pharmaceutical budgets. Although heavily marketed across the UK, there are no long term safety data available and there are concerns that the ubiquity of the enzyme system which they inhibit might predispose to long term safety issues. Many people with diabetes will therefore be moving from one drug with a possible safety problem to another with an unknown long term safety record.

In financially stringent times the extra cost to the health care system of alternative agents may result in rationing of other evidence-based and NICE approved treatments for the management of diabetes.

The most powerful evidence with regard to side effects of pioglitazone come from the PROActive study as it is the only randomised controlled trial. We note that there were more bladder cancers in the pioglitazone group, although this did not achieve significance. There were significantly fewer breast cancers in the pioglitazone group (1). We note that a publication in the current issue of Diabetes Care concerns spontaneous reports of bladder cancer the FDA Adverse Event Reporting System (15). It is of course possible that as it is well known that the link between bladder cancer and pioglitazone is being actively pursued, it is quite likely that bladder cancers are more likely to be reported in pioglitazone treated patients than in non-pioglitazone treated patients.

We note that interim analysis of the Kaiser Permanente longitudinal cohort study found that overall ever use of pioglitazone was not associated with risk of bladder cancer but use for more than 2 years was weakly associated with increased risk (16). This is obviously of concern for long term use. The authors of that paper do acknowledge that there were proportionately more in situ cancers among the pioglitazone users and that this might be observed if pioglitazone-treated patients underwent greater surveillance for bladder cancer.

The French regulatory body have looked at a national database of their own. We suggest the MHRA could consider inviting an interrogation of the UK general practice research database (6) looking side by side at cardiovascular outcomes, bladder and breast cancer and total mortality with regard to the different diabetes therapies.
ABCD wishes to strongly encourage MHRA to resist EMA following the French and German lead with regard to pioglitazone, pending ongoing long-term investigations. While ABCD deems patient safety to be paramount, we are concerned that far more harm than good will be done if pioglitazone is suspended and that on current evidence the risk/benefit balance is strongly in favour of continuing the current licence for the use of pioglitazone to reduce the risks of diabetes-driven morbidity and mortality. In the making of decisions ABCD believes that all factors should be taken into account including macrovascular benefits of pioglitazone, the contribution of pioglitazone to good glycaemic control and associated microvascular benefits and the threat of glycaemic deterioration if pioglitazone is withdrawn. A position aligned with that of the FDA, which recommends withdrawal of pioglitazone only in those with active bladder cancer, and a risk benefit analysis in those with previous cancer, would seem a sensible interim position.

Yours sincerely

Dr Chris Walton, Honorary Chair
Dr Peter Winocour, Immediate Past Chair
Dr Patrick Sharp, Honorary General Secretary
Dr Rob Gregory, Honorary Treasurer
Dr Ketan Dhatariya Honorary Meetings Secretary
Dr Bob Ryder, Committee Member
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Dr C. Walton, Honorary Chairman,
Department of Diabetes, Brocklehurst Building, Hull Royal Infirmary, Hull, HU3 2RW
Email: Chris.Walton@hey.nhs.uk. Tel: 01482 675323


Declaration of interest
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