Royal Colleges must act over Health and Social Care Bill

Despite intense lobbying during its passage through the UK's House of Commons, the Health and Social Care Bill now passes to the House of Lords and will enter into the Committee Stage on Oct 11. We are extremely concerned that, should this legislation be passed, we will be taking yet another step down the road towards a fully private insurance system. The National Health Service (NHS) will be fragmented and its assets will be stripped by private providers looking to run services with profits at the heart of business, not patients.

As junior medical professionals, and as both current and future members of the Royal Colleges, we call on the Royal Colleges to canvas the views of their members to make the necessary representations to the House of Lords while the Health and Social Care Bill is debated and amended.

We encourage the leaders of the Royal Colleges to be bold and vocal in representing the views of their members. This Bill is controversial and has been shown to be widely unpopular, despite an alleged "listening exercise" which failed to lead to any significant rewording of the text in content or meaning. We echo the NHS Consultants' Association's call for a House of Lords Select Committee to scrutinise the Bill and make substantial alterations or halt the Bill, to safeguard the NHS.

Without serious amendments, this legislation will continue to threaten to undermine the NHS by further fragmentation, privatisation, and the introduction of enforced competition by Monitor.[1] Concerns about fragmentation and privatisation have also been publicly expressed by more than 300 public health professionals, including senior directors of public health.[2] These arguments have been iterated many times since the plans were first announced in July, 2010. Plans to involve further private-sector provision is not evidence-based, and doctors' professionalism will be undermined with introductions of conflicts of interest.

We urge the Presidents of the Royal Colleges to use their influence, in what time we have, to safeguard the NHS and ensure that our patients in England can continue to receive a highly cost-effective health service. Our duty of care requires us to do what is best for our patients. Please do not let them down.

We declare that we have no conflicts of interest.

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Pioglitazone and bladder cancer

Pioglitazone, an agonist of the peroxisome-proliferator-activated receptor (PPAR), is a relatively new oral hypoglycaemic drug. Since its first approval in the USA in 1999, a potential link with bladder cancer has been a subject of debate. However, only in September, 2010, did the US Food and Drug Administration (FDA) issue an alert about a potential relation between the occurrence of bladder cancer and the prescription of pioglitazone at high doses for long periods.[1] In April, 2011, Piccini and colleagues,[2] using the FDA Adverse Event Reporting System database, revealed evidence to support a significant risk of bladder cancer associated with pioglitazone irrespective of treatment duration. In July, 2011, the European Medicines Agency issued a warning about the potential for bladder cancer with pioglitazone.[3]

In the PROactive study,[4] published in 2005 by Dormandy and colleagues, 14 (0·5%) cases of bladder neoplasm were reported in the pioglitazone group and six (0·2%) in the placebo group. This difference did not reach significance (p=0·069). In the overview of PROactive data published in 2009,[5] Dormandy and colleagues anecdotally mentioned that, in the placebo group, one case in fact showed a benign histology. This information was presented in the text in brackets, but no new bladder cancer incidence was calculated. We reviewed the PROactive safety data presented in these two publications.

We found that the recalculated overall incidence in the pioglitazone group was statistically greater than in the placebo group: 0·54% (14/2605) versus 0·19% (5/2633), respectively (Fisher's exact test p=0·040). The estimated crude relative risk of bladder cancer was 2·83 (95% CI 1·02–7·85). As in the original article, this incidence did not take into account concomitant potential risk factors or treatment duration. However, this result shows a significant relation between pioglitazone and bladder cancer, which has not been presented in the PROactive study reports.

This finding, associated with the preclinical and clinical findings reported on the FDA website in 2004 (PPAR agonists were claimed to be multispecies, multistrain, multisex, and multisite carcinogens),[6] could have led to an alert 5 years sooner. With this in mind, pioglitazone prescription could have been restricted, and monitoring of patients strengthened. Given the potential loss of opportunity for patients to have been treated otherwise or at least monitored carefully since 2005, vigilance and checking of all relevant safety data reported in clinical trials are crucial.

We declare that we have no conflicts of interest.

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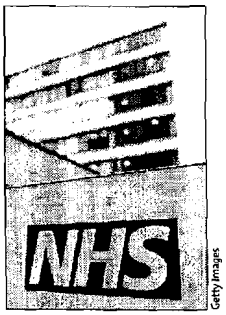

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For the full the full list of signatories see **webappendix**

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In June, 2011, the French and German regulatory bodies suspended pioglitazone over the risk of bladder cancer. The European Medicines Agency (EMA) considered the issue and, on July 21, 2011, concluded that there did seem to be a small increased risk of bladder cancer with pioglitazone.[1] Given this, and concerns about increased fractures and heart failure with pioglitazone,[2] it is not surprising that, in a recent *Lancet* webcast,[3] thiazolidinediones were lumped with sibutramine and rimonabant as drugs that have recently "bombed out". And yet type 2 diabetes is more than anything a disease of people dying prematurely of cardiovascular disease and there is substantial evidence that pioglitazone causes cardiovascular benefit.[2] The widespread blindness to this evidence is attributable to the well known "failure" of the primary composite endpoint in pioglitazone's randomised controlled trial, PROactive.[4] But was this "failure" real?

Table 3 of the original *Lancet* publication of PROactive in 2005[4] shows that the first six factors in PROactive's primary composite endpoint: death, non-fatal myocardial infarction, silent myocardial infarction, stroke, leg amputation, and acute coronary syndrome are all less for pioglitazone than placebo and statistics show significant benefit for pioglitazone. It is only when the bottom two lines in the table—coronary and leg revascularisation—are added in that significance is lost. 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.[2] Thus pioglitazone as an agent of cardiovascular benefit would reduce the need for coronary and leg revascularisation in some patients while increasing the number of patients available for these procedures, making it impossible to come to any conclusion on the basis of procedure-based endpoints.

Pioglitazone reduces glycated haemoglobin (HbA_{1c}) and, by implication, microvascular complications, and substantially reduces the need for insulin.[4] Furthermore, on the basis of the pathophysiology and progress of type 2 diabetes with time, there is a strong case that current ideal management would involve aggressive treatment combining metformin, pioglitazone, and agonists of the glucagon-like peptide 1 receptor with a target HbA_{1c} of less than 42 mmol/mol.[5] It is worth noting that this combination of agents obviates the cost of home glucose monitoring and is devoid of hypoglycaemia risk.

Despite the EMA's conclusion over bladder cancer risk, the overall risk–benefit balance remains strongly in favour of continued use of pioglitazone, especially in patients with ischaemic heart disease (but without heart failure) or stroke.[2]

I have previously received educational sponsorship, speaker fees, and consultancy fees from several pharmaceutical companies including Eli Lilly, GlaxoSmithKline, Novo Nordisk, Sanofi-Aventis, and Takeda.

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Authors' reply

In their letter, Dominique Hillaire-Buys and colleagues draw attention to a potential increase in bladder cancer risk with pioglitazone in PROactive. Although preclinical studies with pioglitazone showed bladder tumours in male rats, none was seen in female rats, mice of either sex, or other organs.[1,2] For pioglitazone, a sex-specific and species-specific mechanism involving formation of urinary solids probably underlies bladder tumour formation in male rats,[3] with good evidence that pioglitazone is not genotoxic.[1,2]

These non-clinical findings did increase awareness of the potential

imbalance of bladder cancer (14 cases on pioglitazone vs six on placebo) seen in PROactive.[4,5] Hillaire-Buys and colleagues correctly note that one placebo case was subsequently classified as benign. This was communicated promptly to regulatory authorities after publication of the PROactive report, and was included in the US product label in August, 2006. After exclusion of cases that occurred within 1 year (as recommended by a masked panel of independent bladder cancer experts owing to biological implausibility), there were six cases for pioglitazone and three for placebo (including the benign case).[5] After further exclusion of those with concomitant risk factors (all smokers and some with multiple risk factors) and the benign case, only two pioglitazone cases and one placebo case remained.[5] These numbers are far too low to suggest a risk imbalance, or to prompt the regulatory actions suggested by Hillaire-Buys and colleagues. Furthermore, overall cancer rates in PROactive were virtually identical in the two treatment groups (4% in each group), and breast cancer was less common with pioglitazone (three vs 11 cases).[5]

To better understand this potential safety signal, Takeda made a commitment to examine any potential long-term bladder cancer risk with pioglitazone. First, a large-scale, 10-year observational study (the KPNC diabetes registry) was begun in 2003. Interim results reported to the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), and published recently,[6] suggest no increased risk of bladder cancer with pioglitazone use overall, with a weak association with longer exposure. Second, an observational follow-up of PROactive is in progress, with interim analyses of cancers submitted every 2 years to the FDA and EMA. During 4 years of follow-up, new bladder cancer cases have in fact been more frequent in patients previously on placebo than in those previously on pioglitazone treatment (unpublished data).

Thus, although the bladder cancer results at the time of the original PROactive publication were not statistically significant, the issue was given appropriate attention during the study, correctly discussed in the publication, and reported to regulatory authorities. Furthermore, appropriate large, long-term studies to investigate this issue are in progress, with regular and full disclosure of results.

Ultimately, any potential for increased risk of bladder cancer with pioglitazone should be considered in the context of overall morbidity in type 2 diabetes. In his letter, Robert Ryder appropriately recognises the high burden of ischaemic cardiovascular disease in patients with type 2 diabetes. In the PROactive population of patients at high cardiovascular risk, there were 58 fewer composite primary endpoint events in the pioglitazone group than in the placebo group.[4] Readers should, however, be reminded that this represented a non-significant 10% reduction in events, thus documenting ischaemic cardiovascular safety with pioglitazone, but not efficacy in reducing events.[4] Other data suggest that these findings extend to lower-risk patients,[7] and mechanistic studies (CHICAGO and PERISCOPE) have shown significantly less progression of the surrogate cardiovascular markers of carotid intima-media thickness and coronary atheroma volume by intravascular ultrasound compared with glimepiride.[8] After the recent very thorough review by the EMA's Committee for Medicinal Products for Human Use (CHMP)[9] of the benefits and risks of pioglitazone treatment, it is reassuring that the benefits outweigh the risks, and that the CHMP states that pioglitazone continues to be a valid option for treating certain patients with type 2 diabetes.

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Guillain-Barré syndrome and H1N1 influenza vaccine in UK children

In 1976, the US National Influenza Immunization Programme (against swine influenza) was discontinued because of an increased risk of