PRIMARY CARE TRUST CHIEF PHARMACIST v TAKEDA

Promotion of Actos and Competact

The chief pharmacist to a primary care trust complained about a promotional 'Dear Healthcare Professional' letter sent by Takeda which was headed with the Competact (pioglitazone/metformin) and Actos (pioglitazone) logos and entitled 'Pioglitazone – An oral anti-hyperglycaemic agent: Summary of beneficial effects on cardiovascular risk and cardiovascular outcomes in Type 2 diabetes'. The letter detailed some of the results from the PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) study (Dormandy *et al* 2005).

The complainant alleged that it was inappropriate to link the study results with cardiovascular benefits as the primary outcome of the PROactive study did not reach statistical significance. The use of secondary endpoints in a negative study had been criticised (Freemantle 2005).

The complainant further alleged that it was misleading to quote adverse effects from a re-analysis of the data rather than the results as originally published which showed increases in heart failure, hospitalisation from heart failure and death from heart failure.

The complainant stated that patients in the PROactive study did not have their cardiovascular medicines optimised – only 40% were on statins. In the group which was on statins, Actos failed to show an advantage.

The Panel noted that at the outset the letter informed readers that the primary endpoint, of the PROactive study, the risk of a composite cardiac outcome, had not reached statistical significance although there was a trend in favour of pioglitazone v placebo. In that regard the Panel did not consider that the PROactive study was a 'negative' study as implied by the complainant. A benefit had been shown for pioglitazone, albeit one that was not statistically significant.

Having explained the primary outcome the letter informed readers that pioglitazone significantly reduced the relative risk of the pre-defined main secondary endpoint, all-cause mortality, MI or stroke. The Panel considered that as the primary endpoint showed a trend in favour of pioglitazone, and the statistical significance of that endpoint had been explained at the outset, it was not misleading to give details of the secondary endpoint. The Panel did not consider the letter was misleading in that regard. No breach of the Code was ruled.

The letter stated 'While the incidence of serious heart failure was higher for pioglitazone-treated vs placebo-treated patients (5.7% vs 4.1%), there was no increase in the incidence of death subsequent to a report of serious heart failure (1.5% vs 1.4%, respectively)'. The Panel noted Takeda's submission that these figures were from the primary analysis of the PROactive study and not from a re-analysis as alleged. The Panel noted the author's comment 'Consistent with the reported side-effect profile for pioglitazone, there was an increased rate of oedema and heart failure, though mortality due to heart failure did not differ between groups'. The Panel considered that the statement in the letter about heart failure was not misleading as alleged and could be substantiated. No breaches of the Code were ruled.

The Panel noted the complainant's concern that only 40% of patients in the PROactive study were on statins and in that regard their cardiovascular therapy was not optimal. Dormandy *et al* noted that study investigators were, however, required, throughout the study, to increase all therapy to an optimum according to the international guidelines. Particular attention was drawn to the need to, *inter alia*, optimise lipid-altering therapy. In that regard the Panel did not consider that patients had not been optimally treated as alleged. The Panel also noted Takeda's submission that statistical analysis showed that baseline, statin-use or non-use, did not predict beneficial response to pioglitazone. This did not support the complainant's statement that, in the groups that were on statins, Actos failed to show an advantage. The Panel did not consider that the letter at issue was misleading in this regard. No breach of the Code was ruled.

The chief pharmacist to a primary care trust complained about a promotional 'Dear Healthcare Professional' letter (ref AC070548) sent by Takeda UK Limited. The letter was headed with the Competact (pioglitazone/metformin) and Actos (pioglitazone) logos and entitled 'Pioglitazone – An oral anti-hyperglycaemic agent: Summary of beneficial effects on cardiovascular risk and cardiovascular outcomes in Type 2 diabetes'. The letter detailed some of the results from the PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) study.

COMPLAINT

The complainant noted that the letter described the PROactive study and linked the study results with cardiovascular benefits. However the complainant alleged this was inappropriate as the primary outcome of the study did not reach statistical significance. The complainant noted that the use of secondary endpoints

in a negative study had been criticised (Freemantle 2005).

The complainant further alleged that it was misleading to quote adverse effects from a re-analysis of the data rather than the results as originally published which showed increases in heart failure, hospitalisation from heart failure and death from heart failure.

The complainant stated that patients in the PROactive study did not have their cardiovascular medicines optimised – only 40% were on statins. In the group which was on statins, Actos failed to show an advantage.

The Authority asked Takeda to respond to the requirements of Clauses 7.2, 7.4, 9.1 and 9.2 of the Code.

RESPONSE

Takeda explained that the letter in question was generated in response to the number of enquiries about the beneficial effects of Actos on cardiovascular risk factors and outcomes and was designed to give health professionals the recent, updated, assessment of these effects as determined by the European Medicines Evaluation Agency (EMEA) and incorporated into the new, revised, European Public Assessment Record (EPAR). In addition, it was designed to draw attention to some recent publications from the PROactive clinical trial, which had appeared in international, peer-reviewed journals, and so allow health professionals to gain further information on this important area.

The letter summarised in an accurate, balanced, fair, and objective manner, some, (but not all) of the beneficial cardiovascular effects and outcomes which had been seen with the Actos in the PROactive study (Dormandy *et al*, 2005) whilst also referring to the cardiovascular adverse effects, ie oedema and heart failure which were acknowledged side effects of Actos, so as to enable health professionals to form their own opinion as to the therapeutic value of using Actos in type 2 diabetics with macrovascular disease.

The letter was posted at the beginning of June, since when the company had received very positive feedback from health professionals who considered it was factual, clear and concise and gave a good overview of both the benefits and the risks. Consequently the company was surprised to receive this one complaint.

Takeda stated that several of the complainant's comments about the PROactive study were either incorrect or at odds with international medical and scientific opinion as given by EMEA, the European Association of the Study of Diabetology (EASD), the PROactive Steering Committee, the authors of three, major international peer reviewed journals, and Takeda.

The integrated medical and statistical study report for the PROactive study was submitted to the EMEA for in-depth regulatory, medical, scientific and statistical assessment at the beginning of 2006. As this assessment would have entailed detailed evaluation by experienced and expert members of the agency over several months, their comments held particular importance in the assessment of the effect of Actos on cardiovascular outcomes.

Takeda explained that the PROactive study was a prospective, randomised, double-blind, multicentre, placebo-controlled, parallel group, phase 3b study involving 5238 with type 2 diabetes and a history of macrovascular disease. The study objectives were primarily; to demonstrate that Actos reduced mortality and macrovascular morbidity in high risk patients with type 2 diabetes compared with placebo and secondarily to further characterise the safety of Actos in this group of patients. The primary endpoint for the study was a composite of 7 different endpoints, 4 of which were disease-led (all cause mortality; non-fatal myocardial infarction (MI) including silent MI, acute coronary syndrome and stroke) and the remaining 3 were procedural (cardiac intervention, major leg amputation and bypass surgery or revascularisation of the leg). The principal secondary endpoint, time to the first occurrence of death from any cause, non-fatal MI (excluding silent MI) and stroke was again a disease-led endpoint, with the two other secondary end points being time to cardiovascular death and the individual components of the primary composite endpoint.

Takeda noted the complainant's comment that it was inappropriate link the results from the PROactive study with cardiovascular benefits because the primary outcome of the study did not reach statistical significance.

The letter stated that '5238 patients were randomised to pioglitazone or placebo in addition to existing and optimised therapies. Those who received pioglitazone showed a 10% relative risk reduction in the primary composite cardiac endpoints compared to placebo, although this did not reach statistical significance'. Thus it was clearly stated in the third paragraph, before any mention of the secondary endpoints, that the primary endpoint for the study was not achieved. Placing this statement first was done so as to comply with the guidance given for 'Advertising: presentation of clinical data' by the Medicines and Healthcare products Regulatory Agency (MHRA) in 2005 which specifically allowed for the promotional use of secondary end points in a study providing:

- The main study endpoint showed some difference in efficacy between the two treatment groups (for PROactive, there was a 10% difference in favour of Actos).
- Presentation of the secondary endpoints was placed within the context of the main primary endpoint (this has been done as stated above).
- The finding of the secondary endpoints were not weak (in PROactive even though all three secondary endpoints showed a beneficial trend in favour of Actos, only those which reached statistical significance were included in the letter).

The letter simply stated that the primary endpoint was not reached. However this finding was explored in more depth by both the PROactive Steering Committee in the initial publication of the study results as well as EMEA

which in the EPAR highlighted that the disease-led (and therefore more important end points) were in Actos' favour, as follows:

> 'Results of the primary composite endpoint analysis showed a 10% relative risk reduction of the first events within the composite for the pioglitazone-treated patients. The COX proportional hazards model gave an estimate of 0.90 for the hazard ratio comparing pioglitazone with placebo which did not reach statistical significance. However, within the primary composite endpoint, fewer disease endpoints (i.e. all cause mortality, non-fatal MI (excluding silent MI) silent MI, stroke, and ACS) were observed in the pioglitazone group, whereas the number of procedural endpoints (cardiac intervention, major leg amputation, leg revascularisation) varied between treatment groups. The only first event that occurred more frequently within the pioglitazone group was leg revascularisation. Overall, there were fewer total endpoints in the pioglitazone group (803) compared with placebo (900).'

Takeda further noted that the complainant had stated that the use of secondary endpoints in a negative study had been criticised by others.

The letter stated that pioglitazone significantly reduced the relative risk of the main secondary endpoint of all cause mortality, non-fatal MI (excluding silent MI) and stroke by 16% as well as two other pre-specified analyses which had been published in international, peer review journals, (Erdmann *et al*, 2007 and Wilcox *et al*, 2007) ie that pioglitazone significantly reduced the occurrence of recurrent MI by 28% (p=0.045) and the occurrence of a recurrent stroke by 47% (p=0.008).

These analyses were also considered by EMEA which commented in the EPAR that;

> 'Results of the analysis of the main secondary composite endpoint, a composite of 3 disease end points of the primary end point (i.e. all cause mortality, non-fatal MI (excluding silent MI) and stroke) showed a statistically significant 16% relative risk reduction of the events within the composite with pioglitazone treatment. The COX proportional hazards model gave an estimate of 0.84 (95% CI: 0.72, 0.98; p=0.0277) for the hazard ratio comparing pioglitazone with placebo…
>
> Subgroup analyses were performed on several pre-specified subgroups based on demographics, medical history, entry criteria, Baseline laboratory values and Baseline medications. The trend of benefit with pioglitazone on the primary and main secondary composite endpoints appeared to be consistent across the subgroups…
>
> Additional endpoints were analysed for the highest risk patients, those with prior MI or prior stroke. Pioglitazone showed a consistent trend of benefit over placebo among patients with prior MI for time to first occurrence of cardiovascular death, non-fatal MI (excluding silent MI), or stroke; cardiovascular death or non-fatal MI (excluding silent MI); and fatal or non-fatal MI (excluding silent MI). For patients with prior stroke, again pioglitazone showed consistent benefit over placebo for the time to first occurrence of cardiovascular death, non-fatal MI (excluding silent MI), or stroke cardiovascular death or stroke; and fatal and non-fatal stroke.'

Furthermore the EPAR referred to several additional analyses which were not mentioned in the mailer on the basis that they had either not been published in international peer review journals or that they were post-hoc and not pre-specified analyses. These were:

> 'Additional "measures of interest" including the composite endpoints of cardiovascular mortality, non-fatal MI (excluding silent MI) or stroke and fatal or non-fatal MI (excluding silent MI) showed statistically significant relative risk reductions of 18% and 23% respectively for pioglitazone-treated patients'
>
> 'The composite endpoints of all-cause mortality, MI (excluding silent MI), stroke, or ACS and of cardiovascular mortality, non-fatal MI (excluding silent MI), stroke or ACS were evaluated. Results of these post hoc analyses for pioglitazone-treated patients were consistent with those seen for the main secondary endpoint showing statistically significant reductions of 17% and 20% respectively, for these composite endpoints.'

Takeda referred to a number of cases where the Panel had reviewed the use of secondary endpoint data in promotional material in situations when the primary endpoint had failed to reach statistical significance. Together the cases supported the position that the results should be consistent across all the pre-defined endpoints, as was the case for the PROactive study. This position was in line with the 2005 guidance from the MHRA and suggested that the promotional use of selected, secondary analyses which did not achieve statistical significance, in the absence of any mention of the primary endpoint, was unacceptable. However, all of the cases suggested that balanced presentation of secondary analyses, alongside full disclosure of the results achieved for the primary endpoint, was acceptable.

In conclusion, even though the primary endpoint did not reach statistical significance Takeda considered it was justified and necessary to mention the beneficial effects which Actos had on some cardiovascular outcomes, in view of the large number of enquiries the company had received.

Takeda noted that following the presentation of the PROactive results at the EASD in 2005, a short article was published in the Education and Debate section of the BMJ (Freemantle). Being a statistician, the author's commentary concentrated on the statistical as opposed to the clinical considerations concerning PROactive, nonetheless he acknowledged the excitement felt by the audience of international diabetolgists when these results were first presented and commented that the 'Consensus of opinion following the presentation' was

that the 'Results would change clinical practice'. The article further stated 'Judgement should be reserved until the results are published in an academic journal' which indeed they were in the Lancet, JACC and Stroke (robust, well respected, peer-reviewed, academic journals) as well as in the new EPAR issued by EMEA. Since his original article, Freemantle had not commented further on the PROactive study.

Takeda noted that the complainant had stated that it was misleading to quote adverse effects from a reanalysis of the data rather than the results as originally published which showed an increase in heart failure, hospitalisation from heart failure, and death from heart failure.

The letter stated that while the incidence of serious heart failure was higher for the pioglitazone- treated v placebo-treated patients (5.7% v 4.1%), there was no increase in the incidence of death subsequent to a report of serious heart failure (1.5% v 1.4% respectively) and came from the primary analyses of the PROactive study, and not the sub-analyses. The primary analyses showed that while the incidence of serious heart failure was higher for Actos-treated patients v placebo (5.7% v 4.1%), there was no increase in the incidence of death due to heart failure with Actos (1.5% v 1.4% respectively). This was of particular importance, for whilst it was recognised that oedema and heart failure were side effects of glitazone therapy, the group of type 2 diabetics studied in the PROactive study were potentially particularly vulnerable to these specific adverse effects as they all had a history of macrovascular disease and almost 50% of them had had a previous MI and so were at risk of compromised cardiac function.

Together with the efficacy data, the safety data was also reviewed by the EMEA, following which a statement was added to section 5.1 of the Actos Summary of Product Characteristics (SPC) as follows 'Although there was an increase in oedema, weight gain and heart failure, there are no long term cardiovascular concerns with the use of pioglitazone and no increase in mortality from heart failure'. In addition, in order to ensure the optimal management of patients in this situation as well as allow for health professionals to make their own judgement as to its therapeutic value the precautionary statement from section 4.4 of the SPC that 'Patients should be observed for signs and symptoms of heart failure as pioglitazone is contraindicated in these patients' was also included. In conclusion the complainant was incorrect in their statements concerning Actos and heart failure.

Takeda noted that the complainant had stated that patients in the PROactive study did not have their cardiovascular medicine optimised - only 40% were on statins. The protocol specifically stated that all patients were to be treated according to the optimised standard of care at that site and in line with the recommendations given in the International Diabetes Federation European Region 1999 Guidelines. This meant that during the course of the study, at months 1, 2, 4, 6, 8, 10 and 12, and thereafter at six-monthly intervals, the investigators were required to optimise all therapy according to the Guidelines as follows; oral glucose-lowering medicine(s) if HbA_{1C}>6.5% and/or fasting venous plasma glucose >6.0mmol/L; insulin if HbA_{1C}>7.5%; a statin if LDL-cholesterol =3mmol/L; a fibrate if triglyceride >2.2mmol/L; lifestyle management followed by antihypertensive(s) if blood pressure >140/85mmHg.

Patients were recruited into the PROactive study between 2001 and 2002 ie before the introduction of the new General Medical Services (GMS) contract in the UK in 2003. Thus at the time, patients in the study were being more optimally managed than those in the general community in the UK, as the International Diabetes Federation Region 1999 Guidelines advocated similar guidance for diabetes dyslipidaemia to that which was later introduced in the GMS contract. The level of statin therapy was similar between groups at baseline (43%), and increased to a similar degree in both groups throughout the study (55% in the Actos-treated group and 55.5% in the placebo group at final visit, p=0.740). Other large, randomised, controlled trials conducted during a similar time period showed a similar trend with regard to the use of statins in patients with type 2 diabetes eg Kahn *et al*, (2006), which randomised patients between 1997 and 2001, showed lipid lowering agents were used in approximately a quarter of patients at baseline, increasing to 45.2%, 48.7% and 55.2% (glyburide, metformin and rosiglitazone groups respectively) at final visit. Furthermore, analysis of UK statin primary care prescribing for type 2 diabetics between 1999 and 2006 showed a similar trend.

Takeda noted the complainant's comment that in the group that was on statins, pioglitazone failed to show an advantage. Statistical analysis showed that baseline, statin-use or non-use, did not predict beneficial response to pioglitazone. The variability between the 25 predefined subgroups of baseline characteristics in terms of cardiovascular outcomes, including the use or non-use of statins at baseline, was no more than expected by chance alone. Therefore, the best estimate of treatment effect for any and all of the subgroups was the same as that for the entire PROactive cohort (Dormandy *et al*).

Dormandy *et al* conducted a multivariate analysis as well as univariate analyses on a number of covariates, including statin therapy. Both of these analyses showed that the trend towards benefit with Actos treatment showed no statistical difference for patients treated with /without existing statin therapy at baseline. Indeed EMEA specifically stated that:

> 'The results of the primary and main secondary endpoints were not affected by adjustment of significant baseline co variants (of which statin use was one) in a multivariate model.
>
> Subgroup analyses were performed on several pre-specified subgroups based on demographics, medical history, entry criteria, baseline laboratory values, and baseline medications. The trend of benefit with pioglitazone on the primary and main secondary composite endpoints appeared to be consistent across the subgroups.'

In conclusion the complainant's statement was not supported by any statistical analysis which had been published or was known to the company and was at odds with general medical, scientific, statistical and regulatory opinion.

Takeda noted that when the PROactive study was presented at the EASD in September 2005 the Association issued a press release which stated that the study:

> '… demonstrated that pioglitazone significantly reduces the risk of heart attacks (also known as myocardial infarction or MI), strokes and death in high risk patients with Type 2 Diabetes. This result is a breakthrough for these patients who are at high risk from heart attacks, strokes or premature death, as it is the first time that an oral diabetes medication has shown significant reductions in these macro-vascular events.'

In the EPAR the EMEA stated:

> 'While the treatment-group difference of 0.5% in the mean HbA_{1C} reduction was statistically significant, it likely cannot entirely explain the cardiovascular benefit noted for pioglitazone.
>
> In PROactive a significant reduction in major cardiovascular events of all-cause mortality, stroke, and myocardial infarction was observed for the pioglitazone-treated group. Events of serious heart failure were reported more frequently in the pioglitazone group than in the placebo group; however mortality was not increased in the pioglitazone-treated patients. A time-to-event analysis of serious heart failure in PROactive showed an increased risk of such an event in the pioglitazone group. However an analysis of time to first event of serious heart failure or all-cause mortality showed that there was no increased risk for this important outcome.'

Indeed even Freemantle stated that consensus of opinion following the presentation was that the 'Results would change clinical practice'.

In conclusion, Takeda stated that the complainant's statements were either factually incorrect, not supported by any statistical analysis, or at odds with the overwhelming medical, scientific, statistical and regulatory assessment of the data. Consequently the company denied that the 'Dear Healthcare Professional' letter at issue contained any misleading information, claims or comparisons or any information which was incapable of substantiation. The letter had been produced to high standards, had not brought the industry into disrepute, and was not in breach of the Clauses 7.2, 7.4, 9.1 or 2.

PANEL RULING

The Panel noted that the 'Dear Healthcare Professional' letter in question detailed some of the results from the PROactive study. At the outset the letter informed readers that the primary endpoint, the risk of a composite cardiac outcome, had not reached statistical significance although there was a trend in favour of pioglitazone v placebo. In that regard the Panel did not consider that the PROactive study was a 'negative' study as implied by the complainant. A benefit had been shown for pioglitazone, albeit one that was not statistically significant.

Having explained the primary outcome the letter proceeded to inform readers that pioglitazone significantly reduced the relative risk of the pre-defined main secondary endpoint, all-cause mortality, MI or stroke, by 16% (p=0.0273). The Panel considered that as the primary endpoint showed a trend in favour of pioglitazone, and the statistical significance of that endpoint had been explained at the outset, it was not misleading to give details of the secondary endpoint. The Panel did not consider the letter was misleading in that regard. No breach of Clause 7.2 was ruled.

The letter stated 'While the incidence of serious heart failure was higher for pioglitazone-treated vs placebo-treated patients (5.7% vs 4.1%), there was no increase in the incidence of death subsequent to a report of serious heart failure (1.5% vs 1.4%, respectively)'. The Panel noted Takeda's submission that these figures had come from the primary analysis of the PROactive study and not from a re-analysis as alleged by the complainant. The Panel noted the author's comment 'Consistent with the reported side-effect profile for pioglitazone, there was an increased rate of oedema and heart failure, though mortality due to heart failure did not differ between groups'. The Panel considered that the statement in the letter about heart failure was not misleading as alleged and could be substantiated. No breach of Clauses 7.2 and 7.4 was ruled.

The Panel noted the complainant's concern that only 40% of patients in the PROactive study were on statins and in that regard their cardiovascular therapy was not optimal. The report on the study (Dormandy *et al*) noted that study investigators were, however, required, throughout the study, to increase all therapy to an optimum according to the International Diabetes Federation European Region 1999 guidelines. Particular attention was drawn to the need to, *inter alia*, optimise lipid-altering therapy. The Panel noted that at baseline, patients in both the pioglitazone and the placebo group had LDL-cholesterol levels of 2.9mmol/L. In that regard the Panel did not consider that the patients in the PROactive study had not been optimally treated as alleged. The Panel also noted Takeda's submission that statistical analysis showed that baseline, statin-use or non-use, did not predict beneficial response to pioglitazone. This did not support the complainant's statement that, in the groups that were on statins, Actos failed to show an advantage. The Panel did not consider that the letter at issue was misleading in this regard. No breach of Clause 7.2 was ruled.

The Panel noted its rulings above and considered that there was no breach of Clauses 2 or 9.1.

Complaint received 15 June 2007

Case completed 8 August 2007