CASE AUTH/2071/11/07

GENERAL PRACTITIONER v TAKEDA

Competact and Actos leavepiece

A general pracationer complained that in a leavepiece for Competact (pioglitazone and metformin) and Actos (pioglitazone) issued by Takeda, data from Lincoff *et al* (2007), a meta-analysis to evaluate the effect of pioglitazone on ischaemic cardiovascular events, was presented in a misleading way. The advantages of pioglitazone were presented in relative risk while the disadvantages were given in terms of absolute risk. If the absolute risk was portrayed as a relative risk then pioglitazone had an increase in serious heart failure of 25-30%.

The Panel noted that the leavepiece contained, *inter alia*, two claims '18% relative risk reduction seen with pioglitazone treatment in the composite primary outcome of mortality, MI or stroke compared to the control group' and further down the page 'The meta–analysis showed an increase in serious heart failure with pioglitazone (2.3% vs 1.8%), but there was no corresponding increase in mortality' both of which were referenced to Lincoff *et al*.

The Panel considered that the presentation of the data in the leavepiece was misleading. To provide one aspect of the information as a reduction in relative risk and another, the risk of serious heart failure, only as an increase in absolute risk was misleading as alleged. It was not made clear that the serious heart failure date represented an absolute risk. A breach of the Code was ruled.

Upon appeal by Takeda the Appeal Board noted the company's submission regarding the way in which risks were conventionally reported in scientific papers, summaries of product characteristics (SPCs) and the like. The leavepiece at issue, however, was a promotional item which thus had to meet the requirements of the Code. The leavepiece had, in effect, condensed the main findings of Lincoff *et al* to one sheet of A4 and in that regard it lacked the additional information which would have otherwise provided a context for the figures reported.

The Appeal Board noted that in the abstract of Lincoff *et al*, the data synthesis section detailed the statistical outcome of the study. The primary composite outcome of death, MI or stroke was reported in terms of absolute risk (4.4% for pioglitazone vs 5.7% for control) with a hazard ratio of 0.82 which had been translated into the leavepiece as an 18% relative risk reduction. The same set of figures was reported for the increased risk of serious heart failure (2.3% for pioglitazone vs 1.8% for control) only in this case the hazard ratio of 1.41 had not been translated into the leavepiece as a 41% relative increased risk. Thus, although the same set of data was reported for the two outcomes they had been reported differently in the leavepiece.

The Appeal Board noted that health professionals knowing only the relative risk of an event or events happening, without also knowing the absolute risks involved, would be unable to judge the clinical impact of the information presented; with regard to the two claims at issue, although readers were told there was a relative risk reduction in mortality, MI and stroke of 18% they were not also told that the absolute reduction was only 1.3%. The Appeal Board considered that it was misleading only to refer to relative risk reduction and upheld the Panel's ruling of a breach of the Code.

A general practitioner complained about a leavepiece (ref AC070946) for Competact (pioglitazone and metformin) and Actos (pioglitazone) issued by Takeda UK Limited. The claims at issue were referenced to Lincoff *et al* (2007) a meta-analysis to evaluate the effect of pioglitazone on ischaemic cardiovascular events which had been published in the Journal of the American Medical Association.

COMPLAINT

The complainant considered that the research data was presented in a misleading way. The advantages of pioglitazone were presented in relative risk reduction. The disadvantages were given in absolute risk reduction. If the absolute risk was portrayed in a relative risk format it meant that pioglitazone had an increase in serious heart failure of 25-30%.

When writing to Takeda, the Authority asked it to respond in relation to Clause 7.2 of the Code.

RESPONSE

Takeda stated that the leavepiece in question was generated in response to enquiries received about the effects of pioglitazone on cardiovascular risk factors and outcomes, following recent media coverage on glitazones and cardiovascular risk. The aim of the leavepiece was to share information from Lincoff *et al* 2007, thus allowing health professionals to gain further information on this important area.

Overall balance in terms of benefit:risk of pioglitazone in the leavepiece

In this respect the key findings of this meta-analysis were described in the highlighted yellow box of the leavepiece and had been specifically written in a sequential order to portray the following:

1 The primary endpoint of the meta-analysis: The beneficial effects of pioglitazone on mortality, myocardial infarction (MI) and stroke, with the statement:

'18% relative risk reduction seen with pioglitazone treatment in the composite primary outcome of mortality, MI or stroke compared with the control group'.

2 The potentially harmful effects of pioglitazone in terms of the associated heart failure that might be seen in some patients. For this, the statement taken from a secondary endpoint of the meta-analysis, was used:

'The meta-analysis showed an increase in serious heart failure with pioglitazone (2.3% vs 1.8%) but there was no corresponding increase in mortality'.

3 A succinct statement regarding the overall benefit:risk assessment with respect to the above three positive and one negative cardiovascular outcomes by means of a direct quote from the author that the results:

'… suggest that the net clinical cardiovascular benefit with pioglitazone therapy is favourable with an important reduction in irreversible events that is not attenuated by the risk of more frequent heart failure complications'.

4 The provision of clear prescribing advice, with the reminder that the presence of heart failure was a specific contraindication so as to ensure appropriate use of the medicine in the appropriate patient population. For this, the statement used was:

'Pioglitazone is indicated for the treatment of hyperglycaemia in type 2 diabetes and is contraindicated for use in patients with heart failure (NYHA class I-IV)'.

Lincoff et al

The stated objective of Lincoff *et al* was 'To systematically evaluate the effect of pioglitazone on ischaemic cardiac events' ie it was not specifically designed to evaluate heart failure. In the data extraction section of the paper, the primary outcome as well as the nature of the ischaemic cardiac events were further defined as 'The primary outcome was a composite of death, myocardial infarction or stroke'. Heart failure was only mentioned in the data extraction section of the abstract in terms of 'Secondary outcomes measures included the incidence of heart failure'. The use of the word 'incidence' was important as it was these incidence figures that were used in the leavepiece. In terms of portraying the potential harmful effects that might be seen with pioglitazone, the phrase 'The meta-analysis showed an increase in serious heart failure with pioglitazone (2.3% vs 1.8%) but there was no corresponding increase in mortality' was used. This succinctly summarised the results given in Table 3 of Lincoff *et al* relating to heart failure. As for the pre-specified secondary end point of 'serious heart failure' the incidence figures were 2.34% and 1.77% for the pioglitazone vs control group respectively, thus giving an absolute difference of 0.57% - numerically much smaller than the absolute difference for the primary endpoint (4.4% vs 5.7 %; 1.3% difference), yet conversely proffering a greater 'relative risk increase' (41%) than seen with the 'relative risk reduction' of the primary endpoint (18%). Thus the combination of two different hazard rates and relative risk reductions would not be appropriate, and could lead to further confusion on a topic that had already caused a lot of confusion with prescribers in 2007.

There had been numerous reports of data and media articles in 2007 on glitazones and associated cardiovascular risks, stemming from a meta-analysis (authored by the same group as this pioglitazone meta-analysis) published in May 2007 (Nissen *et al* 2007). Since then, there had been various reports on both the cardiovascular effects and heart failure for glitazones, which had proved confusing to prescribers. This was reflected by the increased number of enquiries Takeda had received regarding this subject this year. Therefore, Takeda submitted it was important to firstly accurately reflect this new data, whilst also not fuelling the confusion.

Lincoff *et al*, showed an 18% 'relative' risk reduction for the primary outcome and a 41% 'relative' risk increase for serious heart failure, which trended in an opposite direction to the 'absolute' risks for these same endpoints ie 0.57% increased 'absolute' risk for heart failure vs 1.3% reduced 'absolute' risk for the cardiovascular composite endpoint.

Hence for this summary of data depicted as a one-page leavepiece, the heart failure data was represented using the absolute figures only. Takeda believed this accurately reflected Lincoff *et al*, which stated 'This analysis also provides reassuring information that although fluid retention and heart failure are more frequent with pioglitazone treatment; the offsetting risks do not appear to negate the beneficial effects of the drug on irreversible ischaemic and fatal endpoints'.

The data was in-line and reflected the pioglitazone evidence base – eg PROactive showed a similar relative risk reduction for a similar cardiovascular composite endpoint (time to first event of mortality, MI or stroke (except silent MI); relative risk reduction 16% absolute risk reduction: 2.1%) endpoints, whereas the absolute increased risk for heart failure was again in line with that described by the European Medicines Evaluation Agency (EMEA) summary of product characteristics (SPC) which consistently depicted this information as an 'absolute' risk, with the PROactive study showing a 1.6% increase in risk with pioglitazone treatment compared to placebo.

Reference was also made to the combined secondary endpoint of 'Death/serious heart failure' as death was a key component of the combined primary outcome. In this instance the corresponding figures were 4.22% and 4.10% respectively p=0.77.

A recent case (Cases AUTH/1984/4/07 and AUTH/1985/4/07) had also questioned the use of 'relative' risk in instances where it could exaggerate the actual 'absolute' risk, however no breach was ruled.

Need for consistency in the reporting rates of serious heart

failure associated with pioglitazone

The data synthesis section of Lincoff *et al* reported the results for the primary outcome both in terms of absolute values as well as hazard ratios or relative risk reductions. For the heart failure data, the absolute values had also been chosen so as to ensure that they were in accordance with the figures used in PROactive and the SPC hence the statement 'These findings corroborate the results of the PROactive study together with the information in the pioglitazone licences'.

In the PROactive study the incidence of serious heart failure as defined by 'Heart failure requiring hospital admission' was 6% v 4% for pioglitazone v control (ref Table 9 Dormandy *et al*) and in the Actos SPC, Section 4.8 undesirable effects, post marketing data there was a statement 'In controlled clinical trials the incidence of reports of heart failure with pioglitazone treatment was the same as in placebo, metformin and sulphonyurea treatment groups, but was increased when used in combination therapy with insulin. In an outcome study of patients with pre-existing major macrovascular disease, the incidence of serious heart failure was 1.6% higher with pioglitazone than with placebo, when added to therapy that included insulin. However, this did not lead to an increase in mortality in this study'. At no point was there any mention of relative risk.

Reporting of safety information by the EMEA in terms of benefit:risk assessment

Most clinical trials were specifically designed to evaluate the potential clinical benefit that a product might demonstrate in a clearly defined patient population, with the accompanying safety information being collected as a secondary end-point. The primary end-point in clinical outcome studies was generally reported in terms of relative risk reduction and not as absolute risk, as was reflected in the European Public Assessment for pioglitazone where the EMEA in its assessment of pioglitazone in the PROactive study stated that 'The composite endpoints including the primary endpoint excluding silent MI and cardiovascular mortality or non-fatal MI (excluding silent MI) were also evaluated and resulted in relative risk reductions of 10% and 14% respectively for pioglitazone-treated patients, although these reductions were not statistically significant'.

In terms of its assessment of heart failure, the EMEA did not describe this in terms of relative risk reduction as the only statement was that '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 …. Within the cohort of patients receiving insulin at baseline in PROactive, a higher reporting rate of heart failure was seen (6.3% with pioglitazone in combination with insulin vs 5.3% with insulin alone) compared to the total study population (5.1% vs 4.1%)'.

In conclusion

As stated above, in this piece Takeda aimed to share with health professionals information from a recent publication of a meta-analysis of pioglitazone data designed specifically to investigate cardiovascular effects, in order that they would gain further information on this important area. The piece was developed because Takeda had received a large number of enquiries from health professionals about the effects of pioglitazone on cardiovascular risk factors and outcomes following media coverage on the glitazones and cardiovascular risk.

It was certainly never Takeda's intention to try and mislead anyone and it hoped that these comments would explain the thoughts behind the nature and content of the leavepiece and thus allay any concerns that the complainant might have had.

PANEL RULING

The Panel noted that the leavepiece contained, inter alia, two claims '18% relative risk reduction seen with pioglitazone treatment in the composite primary outcome of mortality, MI or stroke compared to the control group' and further down the page 'The meta–analysis showed an increase in serious heart failure with pioglitazone (2.3% vs 1.8%), but there was no corresponding increase in mortality' both of which were referenced to Lincoff *et al*.

The Panel noted that the 18% relative risk reduction in the composite outcome of mortality, MI or stroke was calculated from Lincoff *et al* (Table 3) which also provided the means to calculate the relative increased risk of serious heart failure (41% as submitted by Takeda). The overall absolute risk reduction in the primary end point was given as 4.38 % vs 5.74% and for serious heart failure as 2.34% vs 1.77%. The Panel noted that with regard to heart failure data the SPC did not refer to relative risk.

The Panel considered that the presentation of the data in the leavepiece was misleading. To provide one aspect of the information as a reduction in relative risk and another, the risk of serious heart failure, only as an increase in absolute risk was misleading as alleged. It was not made clear that the serious heart failure date represented an absolute risk. A breach of Clause 7.2 was ruled. This ruling was appealed.

During its consideration of this case the Panel was concerned about the heading 'Pioglitazone is the only glitazone with beneficial effects on cardiovascular risk and cardiovascular outcomes in Type 2 diabetes' in the light of the data on the increase in heart failure. In its view the claim was too general given the data and might be misleading. The Panel requested that the company be advised of its views in this regard.

APPEAL BY TAKEDA

Takeda submitted that the points made in its response still stood and formed part of its appeal. The leavepiece was developed in response to the number of

enquiries which the company had received due to the media coverage on the glitazones and cardiovascular risk and the confusion that existed regarding MI risk (reported with rosiglitazone) and heart failure risk (seen with both glitazones). Takeda had ensured that the overall benefit:risk profile of pioglitazone was represented and as such the key findings from the meta-analysis were presented sequentially. Hence because the stated objective of this meta-analysis was to systematically evaluate the effect of pioglitazone on ischaemic cardiovascular events defined as death, MI or stroke, this information was presented first. The secondary outcome measures included the incidence of serious heart failure and hence the potentially harmful effect of pioglitazone in terms of the incidence of associated heart failure was presented second. This accurately reflected Lincoff *et al* which stated 'This analysis also provides reassuring information that although fluid retention and heart failure are more frequent with pioglitazone treatment, the offsetting risks do not appear to negate the beneficial effects of the drug on irreversible ischaemic and fatal end points'. Next a succinct statement regarding the overall benefit:risk assessment with respect to the above three positive and one negative cardiovascular outcomes by means of a direct quotation from the author was used. Finally a reminder was included that the presence of heart failure was a specific contraindication so as to ensure appropriate use of the medicine in the appropriate patient population. Within the leavepiece a similar amount of space was used to report on the risks as the information on the benefits.

Takeda submitted that it was an accepted convention to use relative risk reduction and absolute risk to describe efficacy and safety/tolerability endpoints respectively. There was only one prospective, cardiovascular outcome study for pioglitazone; PROactive which not only formed part of the meta-analysis referred to above, but was also specifically referred to in the mailer. The results were described in terms of relative risk reduction for all the efficacy data with the safety/tolerability data similarly being given in percentages or absolute values. The statistical basis for this study and calculation of the required patient numbers was based on a projected 20% relative risk reduction between the pioglitazone and placebo treated groups. Consequently the primary endpoint was expressed in terms of hazard ratio/relative risk reduction. In contrast the safety evaluations of serious and non serious events were only shown in terms of percentages/absolute values. At no point was any attempt made to report the adverse effects of pioglitazone treatment in terms of a relative risk increase. The methodological design and results for the PROactive study were reported in Diabetes Care and the Lancet respectively.

Takeda submitted that the internationally acclaimed, landmark study in the field of diabetes was the UKPDS, and the results from this key long-term, prospective, outcomes study had changed treatment paradigms in type 2 diabetes. There had been 78 publications generated from this one study with one of the most important being UKPDS 38, where the effect of good glycaemic and blood pressure control on both micro and macrovascular outcomes was evaluated. In all instances the efficacy results were expressed in terms of relative risk reduction with the safety profile, of the two different treatment regimens, being given in percentages/absolute values.

Takeda submitted that in the EMEA European Public Assessment Record (EPAR) for pioglitazone, the various efficacy results from PROactive – the cardiovascular outcome study, were given in terms of relative risk reduction, yet the safety tolerability data was expressed in terms of percentages. Clearly in their assessment of the risk:benefit of the pioglitazone the regulatory agencies had chosen to use these two different approaches.

Takeda submitted that the Food and Drug Administration's decision to include a black box warning for pioglitazone for heart failure was based on the absolute values or percentages which had been seen in clinical trials for pioglitazone based on treatment regimens vs control therapy. A relative risk increase was never referred to.

Takeda submitted that when the EMEA updated the EPAR for the approval of the new renal indication for Aprovel (irbesartan) the benefit was described in terms of relative risk reduction and the common side effects in terms of incidence rates ie 1 in 10 or 1 in 100 and not relative risk. Finally the adverse effects in section 4.8 of all SPCs were referred to in terms in incidence rates or percentages and not in terms of relative risk with respect to efficacy.

Takeda submitted that it took great care and attention to address all of the matters in the leavepiece in question, in order to ensure it presented the information in a way that clearly showed the risk:benefit profile of the product.

In conclusion, Takeda submitted that as the use of relative risk reductions in clinical outcomes studies was an accepted method for describing efficacy, and the use of percentages or absolute values were accepted for use for the safety tolerability data, the leavepiece was not misleading either directly or by implication and therefore not in breach of Clause 7.2.

COMMENTS FROM THE COMPLAINANT

The complainant stated that he had not changed his opinion. Considering the meta-analysis by Lincoff *et al*, the primary outcome of death/MI/stroke had a hazard ration of 0.82 in favour of pioglitazone which equated to the 18% relative risk reduction in the leavepiece. This statistic was based on absolute risk of 5.7% v 4.4% which equalled an absolute risk reduction of 1.3%. A fair presentation of the data would be to put the advantages and disadvantages in the same format, eg 18% relative risk reduction (absolute risk reduction 1.3%) in death, MI or stroke with pioglitazone vs 41% relative risk of increase (absolute risk of increase 0.5%) in heart failure.

The complainant alleged that the above figures revealed relative risk reduction to be deceptive. The

figures also showed how inappropriate it was to mix relative risk and absolute risk. The selective use of 18% relative risk reduction whilst at the same time giving the disadvantages in absolute terms (for the reader to calculate) was designed to mislead. The benefits of pioglitazone were transparent when viewed in absolute terms.

The complainant appreciated that relative risk measures were widely used in research papers, (as in UKPDS 38) but this did not detract from the fact that relative risk and absolute risk were used as comparators on the same page of a promotional document.

The complainant submitted that the majority of his GP colleagues failed to detect the ambiguity within the statistical measures. When the full picture was explained the usual response was that of annoyance. Unfortunately, absolute and relative risk was not well understood by medical professionals making it difficult for them to apply risk data to individual patients. Consequently the profession was easily misled by relative risk data (McGettigan *et al* 1999). The position taken by Takeda saddened the complainant as it argued that it was common practice and therefore acceptable to juxtapose relative risk and absolute risk. Common practice did not imply right and proper practice. The leavepiece was one example of misleading promotional literature which used relative risk data to bias health professionals towards the prescription of medicines, which was sometimes against the patient's best interests. This problem could be reduced if relative risk data was always accompanied by absolute risk comparators in a standardised format, as illustrated above.

APPEAL BOARD RULING

The Appeal Board noted Takeda's submission regarding the way in which risks were conventionally reported in scientific papers, SPCs and the like. The leavepiece at issue, however, was a promotional item which thus had to meet the requirements of the Code. The leavepiece had, in effect, condensed the main findings of Lincoff *et al* to one sheet of A4 and in that regard it lacked the additional information which would have otherwise provided a context for the figures reported.

The Appeal Board noted that the leavepiece contained, inter alia, two claims '18% relative risk reduction seen with pioglitazone treatment in the composite primary outcome of mortality, MI or stroke compared to the control group' and further down the page 'The meta-analysis showed an increase in serious heart failure with pioglitazone (2.3% vs 1.8%), but there was no corresponding increase in mortality' both of which were referenced to Lincoff *et al*.

The Appeal Board noted that in the abstract of Lincoff *et al*, the data synthesis section detailed the statistical outcome of the study. The primary composite outcome of death, MI or stroke was reported in terms of absolute risk (4.4% for pioglitazone vs 5.7% for control) with a hazard ratio of 0.82 which had been translated into the leavepiece as an 18% relative risk reduction. The same set of figures was reported for the increased risk of serious heart failure (2.3% for pioglitazone vs 1.8% for control) only in this case the hazard ratio of 1.41 had not been translated into the leavepiece as a 41% relative increased risk. Thus, although the same set of data was reported for the two outcomes they had been reported differently in the leavepiece.

The Appeal Board noted that health professionals knowing only the relative risk of an event or events happening, without also knowing the absolute risks involved, would be unable to judge the clinical impact of the information presented; with regard to the above, although readers were told there was a relative risk reduction in mortality, MI and stroke of 18% they were not also told that the absolute reduction was only 1.3%. The Appeal Board considered that it was misleading only to refer to relative risk reduction and upheld the Panel's ruling of a breach of Clause 7.2. The appeal was unsuccessful.

Complaint received	**29 November 2007**
Case completed	**3 April 2008**