CASE AUTH/2164/9/08

MERCK SHARP & DOHME v TAKEDA

Actos and Competact journal advertisement

Merck Sharp & Dohme complained about a journal advertisement for Actos (pioglitazone) and Competact (pioglitazone and metformin) issued by Takeda.

The advertisement consisted of a stylised illustration of an overweight man, over which was superimposed the headline 'ticktock ticktock ticktock ticktock time to act', in large type. The main text consisted of the claim at issue 'Pioglitazone sustains glycaemic control, but that's not all – in an independent meta-analysis, it has also been shown to reduce ischaemic CV [cardiovascular] events in Type 2 diabetes'. A statement detailing the pioglitazone marketing authorization contra-indications in patients with cardiac failure appeared beneath the product logos. Other than the prescribing information and references, the only other text in the advertisement was the statement 'Pioglitazone is indicated for the treatment of hyperglycaemia in Type 2 diabetes' directly beneath the list of references, in the same type-size as the prescribing information and references.

Actos was indicated as monotherapy, or in combination with other therapy, for glycaemic control in type 2 diabetes.

Merck Sharp & Dohme alleged that the claim at issue promoted pioglitazone outwith the terms of its marketing authorization, was unbalanced, misleading, exaggerated and could not be substantiated.

Merck Sharp & Dohme explained that the major causes of mortality and morbidity in type 2 diabetes were the long-term macrovascular (large-vessel) complications of the disease. The ischaemic risk in type 2 diabetes could be significantly reduced by addressing the hypertension and abnormal lipid profile that frequently accompanied diabetes. Far less clear, however, was whether improving glycaemic control had a beneficial effect on overall ischaemic risk.

In assessing the evidence it was important to distinguish between primary outcome trials (conducted in the general diabetes population irrespective of the presence or absence of pre-existing CV risk) and secondary outcome trials (conducted in patients with a prior history of, or recognised as being at greater risk for, ischaemic heart disease).

Merck Sharp & Dohme discussed data from: the United Kingdom Prospective Diabetes Study (UKPDS): three very large outcome trials in type 2 diabetes (ADVANCE, VADT and ACCORD) presented at the American Diabetes Association meeting which examined a variety of treatment strategies, and Takeda's own secondary outcome trial with pioglitazone (PROactive).

Merck Sharp & Dohme noted the following, which were relevant to subsequent arguments:

1 **The claim of a reduction in ischaemic events with pioglitazone was the primary claim and the main, if not the sole, purpose of the advertisement was to place the ischaemic events claim in front of prescribers.**

2 **The whole tenor of the advertisement (the 'ticking clock' theme, the wording 'time to act') implied urgency, that use of pioglitazone might prevent adverse consequences of diabetes and further implied that pioglitazone could reduce the mortality and morbidity attributable to these complications.**

3 **The claim was all-embracing. There was no differentiation between different classes of patients, particularly those with and without increased CV risk and thus it was implied that pioglitazone reduced ischaemic events in the general diabetes population. Substantiation of such an all-embracing claim required robust primary outcome data, or its equivalent.**

4 **The claim was referenced solely to Lincoff *et al* (2007), a meta-analysis described as 'independent' in the advertisement.**

5 **The only description of the licence indications for pioglitazone, other than in the prescribing information, was in the small-font statement below the references.**

Pioglitazone was not licensed to reduce ischaemic events in type 2 diabetes nor mentioned in any section of the summary of product characteristics (SPC).

The advertisement referred to the meta-analysis as 'independent' although Takeda had provided the data for the meta-analysis together with a grant to support the statistical analyses. Whether or not the company had any input into the design or conclusions of the analysis, readers would not conclude from the word 'independent' that the sole financial support for the meta-analysis had been provided by the company whose medicine was under investigation. Merck Sharp & Dohme therefore believed this statement to be misleading.

The detailed response from Takeda is given below.

The Panel noted that Actos was licensed for glycaemic control in type 2 diabetes. There was a difference between promoting a product for a licensed indication and promoting the benefits of treating a condition.

The advertisement featured the outline of an overweight man and running the two pages, and across the man's chest was the statement 'ticktock ticktock ticktock ticktock time to act'. The spacing between successive ticktocks appeared to decrease as if to suggest a clock speeding up with 'time to act' appearing as an alarm call. The Panel considered that some readers would associate the 'ticktock' phrase, particularly given its positioning over the man's chest, with the heart ie 'ticker'. In that regard the Panel considered that the most prominent visual and text of the advertisement suggested cardiovascular issues as opposed to the importance of glycaemic control.

The claim, which ran down the right-hand side of the advertisement, was one continuous statement: 'Pioglitazone sustains glycaemic control but that's not all – in an independent meta-analysis, it has also been shown to reduce ischaemic CV events in Type 2 diabetes'. In that regard the Panel considered that Takeda's description of two claims ('Pioglitazone sustains glycaemic control' followed by a secondary, discursive claim 'shown to reduce ischaemic CV events') with the wording of the second being significantly less prominent than the 'primary claim' was misleading and disingenuous. In the Panel's view the use of the phrase 'but that's not all' suggested that both actions of pioglitazone (glycaemic control and reduction in ischaemic CV events) were of equal importance; some readers would assume that pioglitazone was licensed for both which was not so.

The Panel considered that the claim at issue promoted pioglitazone outwith the terms of its marketing authorization as alleged. The reduction in ischaemic CV events had not been sufficiently clearly placed in the context of being a benefit of glycaemic control. In the Panel's view, given the limited amount of time that people might spend reading a journal advertisement, it was not unreasonable to assume that most readers would read the claim as one simple statement that pioglitazone could be used for glycaemic control and to reduce CV events. A breach of the Code was ruled. On appeal by Takeda the Panel's ruling was upheld by the Appeal Board.

The Panel noted that much of the pioglitazone data in Lincoff *et al* was derived from PROactive which had suggested that treatment was beneficial from the cardiovascular standpoint although significant differences were not observed in the pre-specified primary endpoint (death, myocardial infarction, stroke, acute coronary syndrome, leg amputation or coronary or leg revascularization). Lincoff *et al* stated that their results constituted reasonably strong evidence that pioglitazone reduced the risk of cardiovascular ischaemic endpoints in type 2 diabetes. The Panel noted, however, that the claim at issue, '[pioglitazone] has also been shown to reduce ischaemic CV events in Type 2 diabetes', went further than Lincoff *et al*. The Panel considered that Lincoff *et al* did not substantiate the robust unqualified claim at issue. The claim was misleading in that regard. Breaches of the Code were ruled. On appeal by Takeda the Appeal Board considered that the particular claim regarding the reduction of CV events could be substantiated by Lincoff *et al* and no breach of the Code was ruled.

The Panel noted that the claim referred to Lincoff *et al* as being an independent analysis. At the end of the published paper the authors had acknowledged financial support from Takeda and stated that the company had been involved in the collection of data for the original trials used in the meta-analysis and participated in the identification of adverse events from records within its database. Takeda had provided the database of eligible trials but did not participate in the statistical analyses used for the paper. The company was not involved in preparing the manuscript and was not permitted to review or comment on the content. In the Panel's view Takeda had thus had some involvement in Lincoff *et al* albeit involvement that would not have affected the outcome. Nonetheless the Panel did not consider that describing Lincoff *et al* as independent, in an advertisement, gave the right impression. It implied that Lincoff *et al* was wholly independent of Takeda which was not so. The Panel thus considered that the phrase 'independent analysis', in the context in which it occurred, was misleading as alleged. A breach was ruled which was upheld on appeal by Takeda, the Appeal Board noting that those reading the advertisement would not have the benefit of the declaration of financial support given in the published paper.

Merck Sharp & Dohme Limited complained about a two page journal advertisement (ref AB080313) for Actos (pioglitazone) and Competact (pioglitazone and metformin) issued by Takeda UK Limited which had appeared in Pulse. Inter-company dialogue had failed to resolve the matter.

The advertisement consisted of a stylised illustration of an overweight man, over which was superimposed the headline 'ticktock ticktock ticktock ticktock time to act', in large type. The main text consisted of the claim at issue 'Pioglitazone sustains glycaemic control, but that's not all – in an independent meta-analysis, it has also been shown to reduce ischaemic CV [cardiovascular] events in Type 2 diabetes'. A statement detailing the pioglitazone marketing authorization contra-indications in patients with cardiac failure appeared beneath the product logos. Other than the prescribing information and references, the only other text in the advertisement was the statement 'Pioglitazone is indicated for the treatment of hyperglycaemia in Type 2 diabetes' directly beneath the list of references, in the same type-size as the

prescribing information and references.

Actos was indicated in the treatment of type 2 diabetes mellitus as monotherapy in patients inadequately controlled by diet and exercise for whom metformin was inappropriate due to contraindications or intolerance. It could be used as dual therapy or triple therapy in patients on certain regimes including those with insufficient glycaemic control. Actos could also be used in combination with insulin in type 2 patients with insufficient glycaemic control on insulin for whom metformin was inappropriate due to contraindications or intolerance.

COMPLAINT

Merck Sharp & Dohme alleged that the claim at issue promoted pioglitazone outwith the terms of its marketing authorization, in breach of Clause 3.2, was unbalanced, misleading and exaggerated in breach of Clause 7.2, and could not be substantiated in breach of Clause 7.4.

Merck Sharp & Dohme explained that the major causes of mortality and morbidity in type 2 diabetes were the long-term macrovascular (large-vessel) complications of the disease. These resulted from ischaemic atherosclerotic events, particularly angina, myocardial infarction and stroke. The risk of developing these events was massively increased in type 2 diabetes relative to the general population. It was generally accepted, that the ischaemic risk in type 2 diabetes could be significantly reduced by addressing the hypertension and abnormal lipid profile that frequently accompanied diabetes.

Far less clear, however, was whether improving glycaemic control (ie reducing blood glucose *per se*) had a beneficial effect on overall ischaemic risk. Partly, this was because it was difficult to generate the evidence, as CV outcome trials in type 2 diabetes required large numbers of patients evaluated over many years, and it was often problematic to disentangle the possible contribution of improved glycaemic control from that derived from confounding factors.

In assessing the available evidence, it was important to distinguish between primary outcome trials, ie those conducted in the general diabetes population irrespective of the presence or absence of pre-existing CV risk and secondary outcome trials, ie those conducted in patients with a prior history of, or recognised as being at greater risk for, ischaemic heart disease.

The only primary outcome trial to show any ischaemic heart disease event benefit with an antidiabetic agent was the United Kingdom Prospective Diabetes Study (UKPDS), published over a decade ago. Even here, the improvements in ischaemic heart disease risk were only seen in the subgroup of obese patients treated with metformin (patients treated with other antidiabetic medicines did not show any significant CV outcome benefit). This single finding ensured that metformin was universally recognised in national and international guidelines as the treatment of first choice in type 2 diabetes.

In 2008, three very large outcome trials in type 2 diabetes (ADVANCE, VADT and ACCORD) were presented at the American Diabetes Association meeting. These trials examined a variety of treatment strategies, comparing, as did the UKPDS, intensive vs standard glucose control, but were unable to demonstrate any significant reduction in CV risk with more rigorous blood glucose control.

Takeda's own secondary outcome trial with pioglitazone (PROactive) would be discussed below. However, it should be clear from the above that a claim of a general reduction of ischaemic CV events with an antidiabetic agent would carry extraordinary significance, in effect representing the 'holy grail' of diabetes claims. Were such a claim to be justified and substantiated, it would potentially afford major competitive advantage to the agent concerned. Merck Sharp & Dohme primarily contended that the claim in the advertisement was neither substantiated by the available evidence, nor (even if it were substantiable) justified on the basis of the current pioglitazone marketing authorization.

Merck Sharp & Dohme noted that the following were relevant to subsequent arguments:

1 The claim of a reduction in ischaemic events with pioglitazone was the primary claim made in the advertisement. Of eight lines of text, only two were concerned with glycaemic control, the remainder with ischaemic events. In Merck Sharp & Dohme's opinion, it was clear that the main, if not the sole, purpose of the advertisement was to place the ischaemic events claim in front of prescribers.

2 The whole tenor of the advertisement (the 'ticking clock' theme, the wording 'time to act') implied urgency, that use of pioglitazone might prevent adverse consequences of diabetes. Given point 1, above, this could only mean ischaemic CV consequences, further implying that pioglitazone could reduce the mortality and morbidity attributable to these complications.

3 The claim was all-embracing. No differentiation was made between different classes of patients, particularly those with and without increased CV risk. The reader would inevitably assume that pioglitazone had been shown to reduce ischaemic events in the general diabetes population. Substantiation of such an all-embracing claim would require a primary outcome trial, or its equivalent in terms of robust evidence.

4 The claim was referenced to a single source: Lincoff *et al* (2007), a meta-analysis published in the Journal of the American Medical Association.

5 The meta-analysis was described as 'independent' in the advertisement.

6 The only description of the licence indications for pioglitazone, other than in the prescribing information, was in the small-font statement immediately below the references.

Merck Sharp & Dohme submitted that pioglitazone was not licensed to reduce ischaemic events in type 2 diabetes. Such an effect was neither included in the main indications for pioglitazone, nor in any section of the current summary of product characteristics (SPC), including that on additional pharmacodynamic effects.

In inter-company dialogue, Takeda stated that the PROactive trial, the main component of Lincoff *et al*, had been reviewed by the European licensing authority, and was mentioned in the pioglitazone licence. Leaving aside the fact that the claim was referenced to the meta-analysis as a whole, rather than solely to its PROactive component, examination of the pioglitazone licence revealed that, other than summarising the design of the PROactive trial, the sole licence wording referring to it was as follows:

'Although the study failed regarding its primary endpoint, which was a composite of all-cause mortality, non-fatal myocardial infarction, stroke, acute coronary syndrome, major leg amputation, coronary revascularisation and leg revascularisation, the results suggest that there are no long-term cardiovascular concerns regarding use of pioglitazone. However, the incidences of oedema, weight gain and heart failure were increased. No increase in mortality from heart failure was observed.'

The licensing authority thus undertook a full review of the principal study included in Lincoff *et al* and – while deriving some reassurance concerning the cardiac safety of pioglitazone – did not see fit to include any comment on the effect of pioglitazone on ischaemic event rate other than to state that the study failed its primary endpoint. The inescapable conclusion was that the authority did not view the PROactive results as warranting mention of the CV effects of pioglitazone, even in the high-risk group of patients evaluated, let alone the general diabetes population.

Furthermore, Lincoff *et al* stated in the final paragraph of their publication:

'In conclusion, the findings of this meta-analysis provide evidence of a favorable effect of pioglitazone on ischaemic vascular complications, **which is distinct from the efficacy of thiazolidinediones in reducing blood glucose levels'** [emphasis added].

However, even assuming this to be true, pioglitazone was not licensed for such extra-glycaemic effects. This was recognised in the advertisement by the inclusion of the statement 'Pioglitazone is indicated for the treatment of hyperglycaemia in Type 2 diabetes' under the references.

In summary, even if the claimed reduction in ischaemic events could be appropriately substantiated (which Merck Sharp & Dohme did not believe to be the case), appropriate regulatory scrutiny and amendment of the pioglitazone licence would be necessary before a general promotional claim along these lines could be used. The claim was significant, high-level and all-embracing, and was given clear emphasis above any other claim in the advertisement. As such, it could not be considered as an ancillary effect of the medicine, but as an entirely new indication.

Accordingly, Merck Sharp & Dohme believed that Takeda's promotional use of the claim that pioglitazone reduced ischaemic CV events in type 2 diabetes was not in accordance with the terms of its marketing authorization, in breach of Clause 3.2.

Turning to Lincoff *et al*, Merck Sharp & Dohme did not believe that the data supported a broad and all-embracing claim of ischaemic CV event reduction.

Lincoff *et al* incorporated results from 19 studies the largest of which was PROactive (approximately one-third of all pioglitazone-treated patients). This was also the only study specifically designed to assess CV event rates. Despite the fact that the advertisement was referenced to the meta-analysis as a whole, in inter-company dialogue Takeda emphasised the results from PROactive. Accordingly, Merck Sharp & Dohme began with PROactive and widened the argument out to include the whole meta-analysis. For clarity, Merck Sharp & Dohme had numbered the essential points:

1 PROactive was specifically designed to evaluate the effects of pioglitazone on ischaemic CV events in high-risk patients, ie those with a prior history of CV disease. As such, any results from it, positive or otherwise, could only be applied to that subset of patients, and not to the whole diabetes population.

2 The primary endpoint of the study, a composite of ischaemic CV events and vascular interventions, failed to reach statistical significance. Although some of the subsequent analyses of the secondary endpoints proved to be significant, these findings could only be considered as indicative, rather than definitive.

3 As noted above, the European licensing authority examined all of the data pertaining to PROactive, and, while the results provided some reassurance about the long-term cardiac safety of pioglitazone, the authority evidently did not find the ischaemic event data sufficiently compelling to include them in the pioglitazone licence, even as an additional effect. Indeed, the only comment

it made on the CV event results was that the trial failed to reach its primary endpoint.

4 This lack of data, combined with the regulatory issues, prevented PROactive being used to underpin a general promotional claim in the UK that pioglitazone reduced ischaemic CV event rates in high-risk patients with type 2 diabetes (let alone in diabetics generally).

5 Takeda had implicitly recognised this by not, to Merck Sharp & Dohme's knowledge, using PROactive in this way in any UK promotional materials.

6 Takeda's assertion in inter-company dialogue that Lincoff *et al* 'extends' the findings of PROactive to the general diabetic population was thus disingenuous, as there was no usable claim in high-risk patients to be extended in the first place.

7 Merck Sharp & Dohme noted that PROactive accounted for over 30% of the patients in Lincoff *et al*. Although it was evidently impossible for Merck Sharp & Dohme to perform a full sensitivity analysis on the meta-analysis, it seemed highly probable that PROactive therefore contributed the great majority of the 'positive' data. This was particularly likely as the primary endpoint chosen for Lincoff *et al* was not the composite used as the (failed) primary endpoint in PROactive, but rather one of the secondary PROactive endpoints that did reach significance. As such, majority evidence from a secondary outcome study was being used improperly to support a primary claim.

8 None of the other 18 studies included in Lincoff *et al* were designed or powered to be primary or secondary CV outcome studies. Nine lasted less than 12 months which was an extremely short time to look for CV endpoints, given that the UKPDS took over 10 years to complete. Furthermore, six of the studies included fewer than 200 pioglitazone-treated patients. It was inconceivable that, taken separately or together, these studies could form the basis of any reasonable claim of ischaemic CV event reduction.

9 Takeda sought to make a general, all-embracing claim of ischaemic event reduction with pioglitazone solely based on a single meta-analysis which included, as its main component, a trial which failed to conclusively demonstrate a reduction in high-risk patients, combined with a number of additional trials, none of which were designed to demonstrate this outcome, and many of which were totally unsuitable for this purpose.

In summary, Merck Sharp & Dohme believed that claims of such all-embracing significance required appropriate substantiation; Lincoff *et al* did not represent such evidence. Indeed, the authors acknowledged that the meta-analysis had 'important limitations'. Merck Sharp & Dohme contended that Lincoff *et al* was, at best, hypothesis-generating, and that its preliminary findings would need to be backed up by properly designed randomised controlled trials (and appropriately licensed) before they could support a claim of this kind.

For these reasons, Merck Sharp & Dohme believed that the claim at issue was not capable of appropriate substantiation and that it was thus neither balanced nor fair. Merck Sharp & Dohme alleged breaches of Clauses 7.2 and 7.4.

Merck Sharp & Dohme noted that in the advertisement, the meta-analysis was referred to as 'independent'. However, the paper itself acknowledged that Takeda had provided the data for the meta-analysis together with a grant to support the statistical analyses. Whether or not the company itself had any input into the design or conclusions of the analysis, Merck Sharp & Dohme believed that the readers would not conclude from the word 'independent' that the sole financial support for the meta-analysis had been provided by the company whose medicine was under investigation. Merck Sharp & Dohme therefore believed this statement to be misleading, in breach of Clause 7.2.

In conclusion Merck Sharp & Dohme stated that given the broad significance and misleading nature of the claim at issue, which had been used for several months, the Panel should consider referring this matter to the ABPI Board of Management, with a view to requiring Takeda to issue a formal retraction.

RESPONSE

Takeda did not accept that the reference in the advertisement to the results of an independent meta-analysis were out of context and off balance with the licensed indications for pioglitazone. In view of the overall style and presentation of the different elements of the advertisement, Takeda did not consider that prescribers were likely to regard the main emphasis as being upon ischaemic CV risk reduction nor were likely to be misled into thinking that CV event reduction was claimed as a licensed indication.

The advertisement clearly emphasised the need for, and importance of, glycaemic control in the treatment of type 2 diabetes. The dominant image of a man in the advertisement portrayed a typical person with uncontrolled type 2 diabetes – it did not emphasise or focus upon ischaemic CV risk. Prescribers would immediately recognise that central abdominal obesity in diabetic patients indicated a need for glycaemic control and this was reflected in the advertisement's superscript ('tick tock tick tock … time to act') which provided a 'call to action' in this regard. Therefore, Takeda

considered that the most prominent visual and textual messages before prescribers were those which highlighted the importance of tight glycaemic control in type 2 diabetes. The text at issue, 'reduce ischaemic CV events' was the fourth element in the advertisement – after the visual of the man, the superscript wording of 'tick tock tick tock … time to act', and the primary claim of 'Pioglitazone sustains glycaemic control'. The wording 'reduce ischaemic CV events' was significantly less prominent than either the image of the man, the primary claim and/or the superscript and was explicitly attributed to a meta-analysis, thus making it clear the statement solely presented data from this recent meta-analysis.

Although pioglitazone was not specifically licensed for ischaemic CV event reduction, Takeda noted that the use of CV outcome claims were permitted in promotional material where these were set in the context of the licensed indication (Case AUTH/1340/7/02) and Takeda considered the layout and content of the present advertisement to be consistent with that ruling.

Furthermore, the Medicines and Healthcare products Regulatory Agency (MHRA) in previous dialogue had specifically permitted Takeda to use data from Lincoff *et al* in promotional material, as long as the claim was set in context of any safety concerns. The Authority had previously also ruled to permit claims on ischaemic CV outcomes based upon the PROactive study (Case AUTH/2011/6/07).

The data from Lincoff *et al* was representative of the current evidence base for pioglitazone, and did not conflict with the current evidence base for the management of type 2 diabetes.

Taking all these points into account, as well as the detailed response provided below in part 2, Takeda strongly refuted the allegations that the advertisement breached the Code and/or specifically any of the Clauses 3.2, 7.2 and 7.4.

Takeda noted that Merck Sharp & Dohme had three main concerns, namely that the advertisement promoted pioglitazone outwith the terms of its marketing authorization (alleged breach of Clause 3.2), that the claim at issue was unbalanced, misleading and exaggerated (alleged breach of Clause 7.2) and could not be substantiated (alleged breach of Clause 7.4).

- Alleged breach of Clause 3.2

The advertisement was structured so as to present (visually and textually) the importance of glycaemic control treatment in type 2 diabetes. The text summarised, in an accurate, balanced, fair and objective manner, the licensed indication of sustained glycaemic control with pioglitazone treatment and the result of a recent meta-analysis of pioglitazone data (Lincoff *et al*) so as to enable health professionals to form their own opinions as to the therapeutic value of using the medicine in type 2 diabetics. Taking into account the contraindication for heart failure and the reference to ischaemic CV risk reduction, the advertisement also referred explicitly to this contraindication, drawing prescribers' attention to the necessity for ongoing monitoring of patients, with a view to promoting the rational use of the medicine. Takeda again referred to the rulings made in Cases AUTH/1340/7/02 and AUTH/2011/6/07.

Takeda had recently discussed and agreed the use of ischaemic CV claims, based on Lincoff *et al* and the PROactive data with the MHRA. Takeda gave details of the MHRA's response which were confidential.

The main impact of the advertisement was via the stylised outline of a man and the repeated 'ticktock time to act' superscript. However, the advertisement also contained two less prominent textual claims. The primary claim 'Pioglitazone sustains glycaemic control' based on the licensed indication of pioglitazone. The following, secondary discursive claim 'shown to reduce ischaemic CV events' was explicitly attributed to an identified, independent meta-analysis, making it clear that it was not asserted as a formally licensed indication but was rather based solely upon meta-analysis data. The reference to 'Type 2 diabetes' following the two claims meant that the secondary claim was set explicitly in the context of the management of hyperglycaemia in type 2 diabetics, ie within the licensed indication of pioglitazone.

Merck Sharp & Dohme's central complaint appeared to be that the reference to Lincoff *et al* was not in accordance with the licensed indications for pioglitazone. Takeda disagreed; the main emphasis of the advertisement was clearly upon the need for, and importance of, glycaemic control in type 2 diabetics. The large, stylised image of a man, clearly exhibiting central abdominal obesity, characteristic and typical of a patient with type 2 diabetes, dominated the advertisement. This image therefore immediately portrayed a person whose diabetes was out of control and who needed glycaemic control. The superscript 'ticktock time to act' communicated a 'call to action' to the reader. Therefore, the most prominent visual and textual messages before prescribers clearly highlighted the importance of glycaemic control in type 2 diabetics.

The third level claim at issue was of course significantly less prominent than either the graphic image of the man and/or the superscript. However, the manner of presentation was very different in relation to the other textual claims used in the advertisement. Contrasting language was employed with the licensed indication being clearly stated first and also directly (ie without any attribution): 'pioglitazone sustains glycaemic control' and only after that (effectively as the fourth element in the advertisement), the more discursive follow-on claim: 'in an independent meta-analysis, it has been shown to reduce ischaemic CV events'. The latter was clearly not a primary claim as it started with an

explicit attribution as to its source, which further differentiated these two claims in terms of their impact on prescribers. In view of the overall style and presentation of the different constituent elements of the advertisement, prescribers were neither likely to regard the advertisement's main emphasis as being upon ischaemic CV risk reduction nor to be misled into thinking that the CV event reduction claim was a licensed indication.

Takeda submitted that the patients included within the meta-analysis represented a wide variety of type 2 diabetics, including those with and without established vascular disease, and thus represented a real life type 2 diabetes population. Lincoff *et al* contained a significant proportion of patients from PROactive, ie those at high cardiovascular risk with evidence of previous macrovascular disease. The authors stated that the findings of the meta-analysis 'extend the observations of PROactive in **a larger population and to lower-risk patients without established vascular disease**' (Takeda's emphasis). Tests for heterogeneity performed by Lincoff *et al* showed no difference between shorter and longer term studies, among trials of patients with or without established vascular disease, or importantly, PROactive and all other trials pooled together. Therefore the reference to the conclusions of the meta-analysis in the advertisement did not require any qualification as to patient population.

- Alleged breach of Clause 7.4

The secondary claim in the advertisement *de facto* referred to the primary results of Lincoff *et al*, which was appropriately referenced; as such it was implicit that the claim was substantiated by Lincoff *et al*.

Takeda noted that in Lincoff *et al*, the primary composite end point of death, nonfatal myocardial infarction, or nonfatal stroke occurred in significantly fewer patients on pioglitazone than control (HR, 0.82; 95% CI, 0.72 – 0.94; p=0.005). The authors stated that the primary composite endpoint 'represents irreversible ischemic events and is widely used for cardiovascular outcome trials of chronic therapies' and that 'the current meta-analysis of data from the pioglitazone database presented here constitutes reasonably strong evidence that this agent does, in fact, reduce the risk of cardiovascular ischemic endpoints among patients with Type 2 diabetes mellitus'.

Nineteen trials enrolling 16,390 patients were analysed in the meta-analysis, with pioglitazone treatment lasting from 4 months to 3.5 years. The meta-analysis included patients with uncontrolled type 2 diabetes ie those within the licensed indication. The methods section of Lincoff *et al* clearly explained the type of patients included within the meta-analysis stating 'In general, studies included adult patients with Type 2 diabetes mellitus and inadequate glycemic control. The primary objective of most of the trials was to determine the efficacy of pioglitazone, in combination or comparison with insulin, metformin, sulfonylureas, or rosiglitazone in improving glycemic control'. The studies included in the meta-analysis were therefore fully aligned with the licensed indication for pioglitazone.

Lincoff *et al*, conducted thorough sensitivity analyses, testing for heterogeneity within the studies included to show that the results did not differ with differing variables.

The hierarchy of evidence ranked systemic reviews and meta-analysis as the highest level of evidence. The National Institute for Health and Clinical Excellence (NICE) ranked meta-analysis data as class 1, ie the highest level of evidence. In a guide to interpreting meta-analyses, Davies and Crombie stated: 'The validity of the meta-analysis depends on the quality of the systematic review on which it is based, using both published and unpublished data and where possible using time to first event' and 'Good meta-analyses allow for complete coverage of all relevant studies and look for the presence of heterogeneity and can explore the robustness of the main findings using sensitivity analysis', as was the case for the meta-analysis by Lincoff *et al*.

The European Medicines Evaluation Agency's (EMEA's) guidance stated: 'valuable information has been provided by pooling data from several studies. In the biostatistical guidelines from ICH E9, meta-analytic techniques are recognised as a useful tool to summarise the overall efficacy results of a drug application and to analyse less frequent outcomes in the overall safety evaluation'.

There were a number of accepted regulatory purposes for meta-analysis, including, but not limited to, evaluation of an additional efficacy outcome that required more power than the individual trials could provide.

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) also ranked meta-analysis data highly, having recently updated their joint consensus statement on the management of hyperglycaemia in type 2 diabetes, within which they incorporated Lincoff *et al* to state 'a meta-analysis of the clinical trial data regarding cardiovascular disease risk and pioglitazone has suggested that the drug exerts a protective effect'.

Indeed, recently the EMEA had incorporated the results of meta-analysis conducted by both the manufacturing company (GlaxoSmithKline) as well as the same group as Lincoff *et al* (the Cleveland Clinic, US) to the prescribing information for rosiglitazone-based products to state 'The available data indicate that treatment with rosiglitazone may be associated with an increased risk of myocardial ischaemic events'. These data reported for rosiglitazone had also led to the inclusion of a contra-indication for use in acute coronary syndrome and warnings for use in ischaemic heart

disease and peripheral arterial disease.

The Food and Drugs Administration had also similarly amended its prescribing information with this meta-analysis data, adding an additional black box warning stating 'A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total Patients), most of which compared AVANDIA to placebo, showed AVANDIA to be associated with an increased risk of myocardial ischaemic events such as angina or myocardial infarction'.

Taking all of these points into account, Takeda therefore refuted the allegation of breach of Clause 7.4.

- Alleged breach of Clause 7.2

It was widely accepted that reducing HbA1c (ie the most commonly used and recommended measurement for glycaemic control) was associated with improved ischaemic cardiovascular outcomes. The UKPDS study (UKPDS 35) associated HbA1c reduction with improved cardiovascular outcomes. The study showed every 1% reduction in HbA1c proffered relative risk reductions of 21% for any end point related to diabetes (95% confidence interval 17% to 24%, $p < 0.0001$), 21% for deaths related to diabetes (15% to 27%, $p < 0.0001$), 14% for myocardial infarction (8% to 21%, $p < 0.0001$).

NICE, which could be regarded as representing the body of UK scientific opinion, in its recently updated guidance for the management of type 2 diabetes, evaluated the available data for the relationship between HbA1c and microvascular and/or macrovascular complications and supported the notion that HbA1c reduction was linked to effects on cardiovascular outcomes; it stated: 'Cardiovascular risk can be reduced by 10-15% per 1.0% reduction of HbA1c, the treatment effect and epidemiological analysis of UKPDS giving the same conclusion'.

NICE had also evaluated the Lincoff *et al*, data and stated: 'A meta-analysis of 19 pioglitazone trials (with the PROactive study being the largest study included) reported that treatment with pioglitazone was associated with a significantly lower risk of death, MI, or stroke. Pioglitazone was also associated with a significantly higher risk of serious heart failure'.

Merck Sharp & Dohme's reference to ADVANCE, ACCORD and VADT (not yet published, presented at ADA 68th Scientific Sessions, June 2008) was misleading as these studies did not relate to either pioglitazone or to any of the other studies included in Lincoff *et al* (since none of the studies included in Lincoff *et al* investigated intensive control of glycaemia in type 2 diabetes).

None of the studies identified by Merck Sharp & Dohme were designed to investigate the impact of pioglitazone on cardiovascular disease and therefore the results of these studies were not related to the relevant body of evidence demonstrating the effect that pioglitazone had on ischaemic cardiovascular effects. In particular, Takeda noted:

- VADT did not evaluate pioglitazone usage (only rosiglitazone) and was yet to be published;
- there was only limited pioglitazone usage in ACCORD (90% rosiglitazone use in the intensive arm with only a small proportion using pioglitazone);
- in ADVANCE, the exact pioglitazone usage was not defined though there was only 17% thiazolidinedione use in the intensive arm;
- all of these trials were designed to evaluate intensive vs standard/conventional glycaemic control on a composite of CV outcomes (VADT, ACCORD) or micro-and macrovascular outcomes (ADVANCE) and were not designed to evaluate the effects of any particular therapy;
- the target HbA1c in these trials was much lower than in normal clinical practice and in general the control arms had HbA1c levels closer to those reached in the UK. Thus the treatment arms did not reflect standard UK clinical practice.

In view of the above, Takeda did not consider that the studies identified by Merck Sharp & Dohme undermined or contradicted Lincoff *et al*.

The evidence base for the effects of pioglitazone on ischaemic CV outcomes included Lincoff *et al* as well as PROactive. It was therefore not correct to state that the secondary claim in the advertisement was not appropriately substantiated by current scientific data.

Lincoff *et al* had previously been discussed above.

The primary endpoint for PROactive, which proffered a non-significant reduction with pioglitazone treatment, evaluated a reduction in macrovascular events, including both ischaemic (eg myocardial infarction, stroke) and peripheral (eg amputation, peripheral revascularisation) events. However, the main secondary endpoint and further subsequent analyses of PROactive were specific to ischaemic events, for example, the main secondary endpoint of PROactive evaluated time to the composite of all-cause mortality, myocardial infarction (excluding silent myocardial infarction) and stroke – the same composite evaluated by Lincoff *et al* as the primary endpoint in the meta-analysis showed a significant relative risk reduction for this composite endpoint; with a 16% significant relative risk reduction (2.1% absolute risk reduction) shown in PROactive and an 18% significant relative risk reduction (1.3% absolute risk reduction) in Lincoff *et al*.

Importantly, the European Public Assessment Report (EPAR) published by the EMEA (January

2007), which underlaid the subsequent reference to PROactive in the SPC, explicitly supported the suggestion that there was a trend towards ischaemic benefit seen in the PROactive study. For example, the EPAR stated:

'Results of the analysis of the main secondary composite end point, a composite of 3 disease end points of the primary end points of the primary end point (ie 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 the 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' (Takeda's emphasis).

Takeda noted that promotional claims based upon PROactive, had previously been scrutinised by the Authority and ruled not to be in breach of the Code. In August 2007 a ruling of no breach was made in relation to the use of cardiovascular claims of benefit from PROactive by Takeda in a mailing (Case AUTH/2011/6/07). In this case '... the Panel did not consider the study was a "negative" study the Panel considered that as the primary end point 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 endpoints'.

Other than Lincoff *et al* and PROactive, only one other analysis of ischaemic CV outcomes had been published. This meta-analysis of pioglitazone data had been published by Mannucci *et al* (2008). The meta-analysis included studies not limited to type 2 diabetes and did not utilise patient-level data, whilst evaluating different endpoints to those evaluated by Lincoff *et al*; however, results also showed a trend towards benefit for non-fatal coronary events, which although this was not statistically significant, was nonetheless of a similar magnitude to that seen by Lincoff *et al*.

As clearly laid out in the inter-company correspondence to date, the validity of PROactive data was first questioned by Merck Sharp & Dohme in its initial complaint to Takeda. The discussion that ensued regarding PROactive was merely in response to the concerns raised by Merck Sharp & Dohme. The meta-analysis (which contained a significant proportion of patients from PROactive (32% of the entire population and 55% of patient-years)) alone provided substantiation for the claim of ischaemic event reduction.

Takeda noted Merck Sharp & Dohme's comment that claims of such all-embracing significance required appropriate substantiation, and that Lincoff *et al* did not represent such evidence, the authors having acknowledged the meta-analysis had 'important limitations'.

Takeda noted however that most clinical trials and meta-analysis had 'important limitations' and that Lincoff *et al* immediately followed their comment with 'Nevertheless, because all of the trials used for this analysis were double-blinded and randomized, **potential biases introduced by these limitations should be minimized**' (Takeda's emphasis).

Takeda was concerned that Merck Sharp & Dohme had denigrated the quality of Lincoff *et al*, which underwent a rigorous peer-review prior to publication in the Journal of the American Medical Association (JAMA), a well-respected international journal with a high impact factor. Lincoff *et al* stated: 'A database containing individual patient data collected during eligible clinical trials of pioglitazone was transferred by its manufacturer (Takeda, LincolnShire, Illinois) to the Cleveland Clinic Cardiovascular Coordinating Center, an academic research organization in Cleveland, Ohio, for **independent analysis**' (Takeda's emphasis). Furthermore, the disclosure statement on the manuscript detailed the role of the sponsor as: 'The company (Takeda) had been involved in the collection of data for the original trials used for this meta-analysis and participated in the identification of adverse events from records within their database. The company provided that database of eligible trials to the Cleveland Clinic, and did not participate in the statistical analyses used for this publication. The company was not involved in preparing the manuscript and was not permitted to review or comment on the content'. As Takeda had no involvement in either the review or preparation work for the meta-analysis, it regarded the meta-analysis as independent.

Merck Sharp & Dohme's suggestion that the meta-analysis was not independent was not only derogatory to the Cleveland Clinic, but was also inconsistent with current industry practice of funding academic research by means of 'unrestricted educational grants', whereby funders did not have any involvement in the publication or project involvement. Such funded projects were in Takeda's view, appropriately regarded as independent in view of the lack of control or involvement of the funders. By implication, Merck Sharp & Dohme's suggestion undermined both the credibility of academic organizations and healthcare institutions which accepted such unrestricted grants from the pharmaceutical industry as well as the output of such past and future support. To suggest that pharmaceutical companies inappropriately influenced activities which were carried out under unrestricted educational grants risked seriously discrediting and reducing confidence in the pharmaceutical industry as a whole and also ignored the real scientific and patient benefits which flowed from such industry support. Takeda did not endorse Merck Sharp & Dohme's approach and considered that the company should retract its insinuations regarding the Cleveland Clinic.

In view of the arguments set out above Takeda refuted the allegation that the advertisement breached Clause 7.2.

PANEL RULING

The Panel noted Takeda's submissions regarding previous cases and/or previous claims for pioglitazone. In that regard the Panel noted that it considered every case on its own merits. Case precedents were helpful but the complaint made and the material at issue were extremely important and previous rulings of no breach of the Code did not guarantee the same rulings in future with regard to different complaints and different material.

The Panel noted that Actos was licensed for glycaemic control in type 2 diabetes. There was a difference between promoting a product for a licensed indication and promoting the benefits of treating a condition.

The Panel noted that the advertisement at issue featured the outline of an overweight man and running the two pages, and across the man's chest was the statement 'ticktock ticktock ticktock ticktock time to act'. This was the dominant image in the advertisement. The spacing between successive ticktocks appeared to decrease as if to suggest a clock speeding up with 'time to act' appearing as an alarm call. The Panel considered that some readers would associate the 'ticktock' phrase, particularly given its positioning over the man's chest, with the heart ie 'ticker'. In that regard the Panel considered that the most prominent visual and text of advertisement suggested cardiovascular issues as opposed to the importance of glycaemic control as submitted by Takeda.

The claim, which ran down the right-hand side of the advertisement, was one continuous statement: 'Pioglitazone sustains glycaemic control but that's not all – in an independent meta-analysis, it has also been shown to reduce ischaemic CV events in Type 2 diabetes'. In that regard the Panel considered that Takeda's description of two claims ('Pioglitazone sustains glycaemic control' followed by a secondary, discursive claim 'shown to reduce ischaemic CV events') with the wording of the second being significantly less prominent than the 'primary claim' was misleading and disingenuous. There was only one claim, all in the same font size and the two components were clearly linked. In the Panel's view the use of the phrase 'but that's not all' suggested that both actions of pioglitazone (glycaemic control and reduction in ischaemic CV events) were of equal importance; some readers would assume that pioglitazone was licensed for both which was not so.

The Panel considered that the claim at issue promoted pioglitazone outwith the terms of its marketing authorization as alleged. The reduction in ischaemic CV events had not been sufficiently clearly placed in the context of being a benefit of glycaemic control. In the Panel's view, given the limited amount of time that people might spend reading a journal advertisement, it was not unreasonable to assume that most readers would read the claim as one simple statement that pioglitazone could be used for glycaemic control and to reduce CV events. A breach of Clause 3.2 was ruled.

The Panel noted that much of the pioglitazone data in Lincoff *et al* was derived from PROactive which had suggested that treatment was beneficial from the cardiovascular standpoint although significant differences were not observed in the pre-specified primary endpoint (death, myocardial infarction, stroke, acute coronary syndrome, leg amputation or coronary or leg revascularization). Lincoff *et al* stated that their results constituted reasonably strong evidence that pioglitazone did reduce the risk of cardiovascular ischaemic endpoints in type 2 diabetes. The Panel noted, however, that the claim at issue stated: '[pioglitazone] has also been shown to reduce ischaemic CV events in Type 2 diabetes'. In that regard the claim went further than Lincoff *et al*. The Panel considered that Lincoff *et al* did not substantiate the robust unqualified claim at issue. The claim was misleading in that regard. Breaches of Clauses 7.2 and 7.4 were ruled.

The Panel noted that the claim referred to Lincoff *et al* as being an independent analysis. At the end of the published paper the authors had acknowledged financial support from Takeda and stated that the company had been involved in the collection of data for the original trials used in the meta-analysis and participated in the identification of adverse events from records within its database. Takeda had provided the database of eligible trials but did not participate in the statistical analyses used for the paper. The company was not involved in preparing the manuscript and was not permitted to review or comment on the content. In the Panel's view Takeda had thus had some involvement in Lincoff *et al* albeit involvement that would not have affected the outcome. Nonetheless the Panel did not consider that describing Lincoff *et al* as independent, in an advertisement, gave the right impression. It implied that Lincoff *et al* was wholly independent of Takeda which was not so – the study had been funded by Takeda and the company had provided or helped to provide some of the data. The Panel thus considered that the phrase 'independent analysis', in the context in which it occurred, was misleading as alleged. A breach of Clause 7.2 was ruled.

With regard to Merck Sharp & Dohme's request that the Panel refer the matter to the ABPI Board of Management with a view to requiring Takeda to issue a retraction, the Panel noted that it could not refer the matter to the ABPI Board. The Appeal Board could require publication of a corrective statement but the Panel could not.

APPEAL BY TAKEDA

Takeda submitted that the advertisement was devised to highlight the importance of glycaemic

control in type 2 diabetes, conveying the need to act for the many patients that were uncontrolled, and to enable health professionals to form their own opinions as to the therapeutic value of using pioglitazone. It was developed to provide the most recent evidence with pioglitazone, at a time when uncertainty existed for health professionals of the glitazone class due to the media coverage on the glitazones and myocardial infarction risk (reported with rosiglitazone) and heart failure risk (seen with both glitazones). Thus the advertisement was designed to clarify the efficacy and safety profile of pioglitazone.

Takeda submitted that it took care to ensure that the overall benefit:risk profile of pioglitazone was represented and that it was clear to the reader that it was first and foremost used for, and licensed in, glycaemic control (as per previous case precedent). The claim regarding reductions in ischaemic CV events was specifically attributed and substantiated by an independent meta-analysis conducted by Lincoff *et al* in which the authors concluded 'the findings of this meta-analysis provide evidence of a favorable effect of pioglitazone on ischemic vascular complications'. More recently Lincoff *et al* had been reviewed by leading independent medical bodies ADA, EASD and NICE), which supported its findings (Nathan *et al* 2008).

The meta-analysis was recognised as independent by the authors ('A database containing individual patient data collected during eligible clinical trials of pioglitazone was transferred by its manufacturer (Takeda, Lincolnshire, Illinois) to the Cleveland Clinic Cardiovascular Coordinating Center, an academic research organization in Cleveland, Ohio, for **independent analysis**.') [emphasis added] who confirmed that whilst Takeda had provided patient level data and funding, it did not participate in the statistical analyses, or in preparing the manuscript and furthermore it was not permitted to review or comment on the contents.

Takeda's understanding of the Panel's ruling was that, consistent with previous case precedent, claims pertaining to additional effects, eg ischaemic CV outcomes data, were acceptable in promotional material. However, its concerns arose surrounding the balance of presentation of the licensed indication and additional effects, the specific wording used in the advertisement to describe the conclusions of Lincoff *et al*, and the use of the word 'independent' to describe the meta-analysis.

Takeda submitted that the points made in its response to the complaint still stood. The key points were as follows

1 Balance of representation of the licensed indication (glycaemic control) and additional ischaemic CV effects – breach of Clause 3.2

Takeda submitted that the interpretation of the visuals and copy was subjective to the reader. During the development of the advertisement, Takeda tested the concept on a number of health professionals to ensure its intention came across correctly in the advertisement. Takeda's intention for the advertisement was as follows.

The visual was typical of a patient with type 2 diabetes, with the 'ticktock ticktock' theme representative of a 'call to action' for the health professional to act, ie it suggested time passing. In the UK, a vast number of patients with type 2 diabetes were uncontrolled and would benefit from a change in, or an additional, medication (for example, the quality outcomes frame work (QOF) target in England for achievement of the HbA1c target of ≤ 7.5 was found to be only 66.8% in 2007/08, thus leaving a large population not achieving this audit target (Lincoff *et al*)). The design of the visual, was so that 'ticktock ticktock' emphasised this impending need to manage the progression of the disease, and drew attention first to the man, typical of a patient with type 2 diabetes, and then to the headline 'time to act' followed by the copy, brand names and heart failure warnings. Therefore, the 'ticktock ticktock' wording was used to firstly position the theme of time and secondly to link from the visual to the copy.

The 'ticktock ticktock' line was not designed with decreasing gaps, as suggested by the Panel. The gaps were designed for readability, as the wording spanned the man's body as well as the centrefold of the journal.

First and foremost, the claim stated that pioglitazone sustained glycaemic control – this was first, before any statement about ischaemic CV effects. The advertisement then went on to state 'but that's not all – in an independent meta-analysis, it has also been shown' – to ensure the reader saw the claim that followed (to reduce ischaemic CV events) was supported by the meta-analysis and not specifically attributed to the SPC, thus being in the context of the licensed indication (glycaemic control).

The basis for the claim on ischaemic CV event reduction was Lincoff *et al*, with the claim specifically attributed to the Lincoff *et al* meta-analysis, rather than appearing as a claim from the SPC. This was to ensure there was a clear separation from the licensed indication and any additional benefits seen on ischaemic CV events.

All the patients in the meta-analysis had uncontrolled type 2 diabetes (ie the observed CV effect was in patients with a licensed indication for pioglitazone's use). Takeda therefore considered the follow-up claim of ischaemic CV event reduction was adequately set in the context of glycaemic control.

It was widely recognised that the main purpose of glycaemic control was to reduce the risk of

complications (NICE). It had been noted that 80% of patients with type 2 diabetes would die prematurely from CVD (Barnett *et al* 2003), therefore it was especially important for prescribers to know of any additional evidence that confirmed this benefit with an oral anti-hyperglycaemic agent.

2 The robustness and validity of using Lincoff *et al* to substantiate the claim 'shown to reduce ischaemic CV events' – breaches of Clauses 7.2 and 7.4

Takeda submitted that the Panel's statement that 'Lincoff *et al* stated that their results constituted reasonably strong evidence that pioglitazone did reduce the risk of ischaemic cardiovascular ischaemic endpoints in type 2 diabetes' differed from the conclusions given by Lincoff *et al*. This stated 'Pioglitazone is associated with a significantly lower risk of death, myocardial infarction or stroke among a diverse population of patients with diabetes' and 'In conclusion, the findings of this meta-analysis provide evidence of a favorable effect of pioglitazone on ischemic vascular complications'. Therefore, the wording in the advertisement, that 'it has also been shown to reduce ischaemic CV events' reflected and did not go further than Lincoff *et al*. Lincoff *et al* did not state that the evidence was 'reasonably strong' as suggested by the Panel.

The meta-analysis was conducted by the Cleveland Clinic in the US. The Cleveland Clinic Lerner Research Institute was the fifth largest research institute in the US and in 2007, research from the Cleveland clinic appeared in 1,196 publications, including 1,060 journal articles, 126 book chapters and 10 books. Many of these were in highly respected peer-reviewed high-impact journals, as was the meta-analysis in question which was published in JAMA.

A similar meta-analysis conducted by the Cleveland Clinic (which was slightly less robust in design as patient level data was not available for analysis) for rosiglitazone had been widely publicised (Nissen *et al* 2007) and having been reviewed by regulatory authorities in the US and Europe had resulted in licence changes for rosiglitazone issued by the FDA and the EMEA. Other meta-analyses conducted by the same group had resulted in medicines being withdrawn from development (eg muraglitazar (Nissen *et al* 2005)) or from the market (Vioxx (Nissen *et al* 2001)). Both meta-analyses evaluating muraglitazar and Vioxx were published in the same journal as Lincoff *et al*, ie JAMA.

Takeda had recently discussed and agreed the use of ischaemic CV claims, based on the Lincoff *et al* with the MHRA which confirmed that it was acceptable to make claims relating to ischaemic CV events from this study, providing they were placed in context of safety, with guidance detailed on the monitoring requirements for heart failure and the contraindication for use in heart failure (all of which was included in the advertisement in question).

A number of independent medical and scientific bodies had recently reviewed the data from Lincoff *et al*:

NICE recently issued updated draft guidance for consultation on newer agents in the management of type 2 diabetes. The guidelines development group (consisting of leading UK experts in diabetes), reviewed the Lincoff *et al* data and stated 'One meta-analysis (Lincoff *et al* 2007) showed a reduced risk of death, myocardial infarction or stroke associated with the use of pioglitazone' and 'the current evidence suggests that rosiglitazone increases the risk of heart attacks and cardiovascular mortality but that pioglitazone reduces it'. The ADA and EASD recently issued an updated consensus statement on the management of type 2 diabetes, having reviewed the ischaemic CV outcomes data (including Lincoff *et al*); they also recognised 'a potential decrease in MI' with pioglitazone (Nathan *et al*).

3 Was Lincoff *et al* independent?

Lincoff *et al* stated: 'A database containing individual patient data collected during eligible clinical trials of pioglitazone was transferred by its manufacturer (Takeda, Lincolnshire, Illinois) to the Cleveland Clinic Cardiovascular Coordinating Center, an academic research organization in Cleveland, Ohio, for **independent analysis**' [emphasis added].

Furthermore, the disclosure statement detailed the role of the sponsor as: 'The company [Takeda] had been involved in the collection of data for the original trials used for this meta-analysis and participated in the identification of adverse events from records within their database. The company provided that database of eligible trials to the Cleveland Clinic, and did not participate in the statistical analyses used for this publication. The company was not involved in preparing the manuscript and was not permitted to review or comment on the contents'.

In view of the absence of any company involvement in either the review or preparation work for the meta-analysis, ie in any of the work fundamental to the meta-analysis, Takeda regarded the meta-analysis as independent.

The suggestion that the meta-analysis was not independent was inconsistent with current industry practice of funding academic research by means of 'unrestricted educational grants', whereby funders did not have any involvement in the publication or project involved. Such funded projects were appropriately regarded as independent in view of the lack of control or involvement of the funders. Indeed, regulatory bodies like the EMEA, received funding and patient level data from pharmaceutical

companies but its independence in evaluation of the data was not in question.

The Panel ruling acknowledged that Takeda had no influence over the outcome or publication of the meta-analysis in its ruling; that Takeda had thus had some involvement in Lincoff *et al*, **albeit involvement that would not have affected the outcome** [emphasis added]. Takeda submitted that this was the most important criterion for whether or not the word independent could be reasonably used.

The suggestion that the meta-analysis was not independent challenged the practice of academic organisations and healthcare institutions in receiving unrestricted grants from the pharmaceutical industry as well as the output of such past and future support. To suggest that pharmaceutical companies inappropriately influenced activities which were carried out under unrestricted educational grants risked reducing confidence in the pharmaceutical industry as a whole.

In conclusion, Takeda emphasised that it was fully committed to compliance with both the letter and the spirit of the Code and had carefully considered the Panel's rulings. It took great care and attention in the preparation of the advertisement in order to ensure that it presented the information in a way that clearly showed the licensed use for pioglitazone before, and above, the additional claim regarding ischaemic CV events. This was further supported by the clear attribution of the additional claim to the independent meta-analysis by Lincoff *et al*. Therefore, Takeda strongly refuted any breaches of the Code.

COMMENTS FROM MERCK SHARP & DOHME

Merck Sharp & Dohme stated that the basis of its case remained as set out in its complaint. However, it would address briefly some of the issues raised by Takeda in its appeal.

1 Balance of advertisement and promotion outside the licence

Merck Sharp & Dohme fully concurred with the Panel's ruling concerning the inappropriate balance of the advertisement, particularly considering the font size, style, graphics, and specific wording of the claim in question. Merck Sharp & Dohme alleged that the clear primary purpose of the advertisement was to communicate the purported effect of pioglitazone on ischaemic heart disease and that this would be the natural inference drawn.

The average reader of the advertisement would be led to believe that Actos and Competact were licensed to reduce the incidence of ischaemic heart disease, in contrast to the position with other treatments for type 2 diabetes. Takeda's appeal, concentrated on the 'balance' arguments referred to above, ignored one of Merck Sharp & Dohme fundamental areas of concern: even if the balance of the claims in the advertisement were more appropriate, and even if they could be more robustly substantiated, Merck Sharp & Dohme alleged that Takeda would not be justified under the Code in making ischaemic heart disease reduction claims for pioglitazone within the terms of its current licence.

While ischaemic heart disease was a well-recognised long-term complication of type 2 diabetes, it was not the same disease entity. Pioglitazone was licensed only for glycaemic reduction in type 2 diabetes, and not for prevention of ischaemic heart disease. The pioglitazone SPC did not refer to any beneficial effects of pioglitazone on ischaemic heart disease status. The relationship between improvements in glycaemic control and reduction in ischaemic heart disease rate remained controversial, certainly within the time-frames of the studies included in Lincoff *et al*. Finally, Lincoff *et al* specifically stated that the effect of pioglitazone on ischaemic heart disease, if real, 'is distinct from the efficacy of thiazolidinediones in reducing blood glucose levels', whereas pioglitazone did not have a licence for any such extra-glycaemic effect.

Should there be sufficient evidence to warrant ischaemic heart disease reduction claims, this evidence should be submitted to the appropriate regulatory authorities with a view to securing a licence amendment. As matters stood, there was a considerable history of claims concerning the 'ancillary' effects of products coming before the Panel and Appeal Board, particularly in the therapy area of diabetes. Merck Sharp & Dohme therefore asked the Appeal Board to make an explicit judgement on this matter, if only to avoid the necessity for such cases in the future.

2 Heart failure

Merck Sharp & Dohme noted that Takeda had stated in its appeal that the advertisement was designed to clarify the efficacy and safety profile of pioglitazone. It also explicitly mentioned the current uncertainty of health professionals regarding the heart failure risk seen with glitazones.

Merck Sharp & Dohme's concerns about the issue of heart failure were expressed in its complaint, but were not considered by the Panel, as they had not been subject to adequate inter-company dialogue. However, since this issue had been raised by Takeda at appeal, Merck Sharp & Dohme alleged that the meta-analysis on which the ischaemic heart disease claim was based also noted a significant increase in heart failure incidence in pioglitazone-treated patients. In fact, this finding had a lower p-value than the ischaemic heart disease data. By focussing solely on the positive aspects of the meta-analysis, the

advertisement did not accurately present the totality of the data with respect to important issues of patient safety, and was therefore biased and misleading, representing a further and separate breach of Clause 7.2. As this focussed on one particular positive aspect of the data it did not encourage rational prescribing, and was directly related to patient safety, Merck Sharp & Dohme considered the issue to be of the utmost seriousness.

3 Substantiation

Merck Sharp & Dohme noted Takeda's comments concerning reactions to Lincoff *et al* and similar meta-analysis. Merck Sharp & Dohme alleged that the situation was, however, far less clear-cut than these comments suggested. In fact, there was intense controversy within the diabetes community with respect to the significance, validity, applicability and implications of both the rosiglitazone and pioglitazone meta-analyses.

That said, the true issue in question was whether, under the Code, Takeda was justified in making all-embracing claims on the basis of a single meta-analysis involving often clearly inappropriate studies, none of which were designed or powered to demonstrate the primary outcome benefit being claimed. Although Merck Sharp & Dohme had no objection in general to the appropriate use of meta-analysis data in supporting product claims, Lincoff *et al* alone did not adequately substantiate the claim in question.

4 Use of the word 'independent'

By questioning the use of the word 'independent' in reference to Lincoff *et al*, it was not, of course, Merck Sharp & Dohme's intention to impugn in any way the integrity of the academic centre that performed the analysis. The fact that Takeda supplied the centre with all the data used in the analysis, in itself, rendered the description of 'independent' inappropriate. Further, there was a widely acknowledged general perception that studies could not be considered as truly independent if they were wholly funded by the organisation whose product was being investigated.

Merck Sharp & Dohme had no reason to doubt that the meta-analysis was conducted by the centre concerned with all due ethical and scientific rigour. This did not alter the fact that there were well-defined expectations attached to the use of such terms as 'independent'. These expectations were patently not met in the present case, and Merck Sharp & Dohme therefore maintained that the use of the term in the advertisement was improper and misleading.

In light of the above, and the detailed representations made in its complaint, Merck Sharp & Dohme asked the Appeal Board to uphold the Panel's rulings.

Merck Sharp & Dohme noted that in its original submission, it asked the Panel to consider referring the case to the ABPI Board of Management with a view to requiring Takeda to issue a formal retraction of the claims made in the advertisement, together with a corrective statement. The Panel informed Merck Sharp & Dohme in its ruling that only the Appeal Board could so act. Given that this matter was now before the Appeal Board and in the event that the Appeal Board upheld the Panel's rulings, Merck Sharp & Dohme reiterated its request that further sanctions be considered, particularly in view of the length of time that health professionals had been exposed to these materials.

APPEAL BOARD RULING

The Appeal Board noted there was a difference between promoting a product for a licensed indication and promoting the benefits of treating a condition.

The Appeal Board examined the advertisement at issue which featured the outline of an overweight man and running across the two pages, and across the man's chest, and thus his heart, was the statement 'ticktock ticktock ticktock ticktock time to act'. This was the dominant image in the advertisement. The spacing between successive ticktocks appeared to decrease as if to suggest a clock speeding up with 'time to act' appearing as an alarm call. The Appeal Board considered that some readers would associate the 'ticktock' phrase, particularly given its positioning over the man's chest, with the heart ie 'ticker'. In that regard the Appeal Board considered that the most prominent visual and text of the advertisement suggested cardiovascular issues as opposed to the importance of glycaemic control as submitted by Takeda.

The Appeal Board considered that the claim at issue, which ran down the right-hand side of the advertisement, 'Pioglitazone sustains glycaemic control, but that's not all – in an independent meta-analysis, it had also been shown to reduce ischaemic CV events in Type 2 diabetes'. was one continuous statement, and not two claims ('Pioglitazone sustains glycaemic control' followed by a secondary, discursive claim 'shown to reduce ischaemic CV events') as submitted by Takeda. The entire claim was the same font size and the two components were clearly linked. The Appeal Board considered that some readers would therefore assume that pioglitazone was licensed for both glycaemic control and reduction of ischaemic CV events which was not so.

The Appeal Board considered that the claim at issue together with the visual promoted pioglitazone outwith the terms of its marketing authorization as alleged. The reduction in ischaemic CV events had not been sufficiently clearly placed in the context of being a benefit of

glycaemic control. It was not unreasonable to assume that most readers would read the claim as one simple statement: that pioglitazone could be used for glycaemic control and to reduce CV events. The Appeal Board upheld the Panel's ruling of a breach of Clause 3.2. The appeal on this point was unsuccessful.

The Appeal Board considered that the undue emphasis placed on the reduction of ischaemic CV events by pioglitazone was misleading and it upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

The Appeal Board considered that the particular claim regarding the reduction of CV events was capable of substantiation by Lincoff *et al*. Thus the Appeal Board ruled no breach of Clause 7.4. The appeal on this point was successful.

The Appeal Board noted that the particular claim referred to Lincoff *et al* as an independent meta-analysis. At the end of the published paper the authors had acknowledged financial support from Takeda. Takeda had provided the database of eligible trials but did not participate in the statistical analyses used for the paper. The company was not involved in preparing the manuscript and was not permitted to review or comment on the content. In the Appeal Board's view Takeda had no involvement in Lincoff *et al* that would have affected its scientific rigour and outcome. Nonetheless describing Lincoff *et al* as independent, in the advertisement, gave a misleading impression. Those reading the advertisement would not have the benefit of the declaration of financial support given in Lincoff *et al*. The claim implied that Lincoff *et al* was wholly independent of Takeda which was not so – funding and data had been provided by Takeda and this would not be clear from the use of the word 'independent' in the advertisement. The Appeal Board thus considered that the phrase 'independent meta-analysis', in the advertisement, was misleading as alleged. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2.

The Appeal Board did not consider the circumstances warranted additional sanctions as requested by Merck Sharp & Dohme.

Complaint received **1 September 2008**

Case completed **16 February 2009**