CASE AUTH/2125/5/08

# GLAXOSMITHKLINE v TAKEDA EUROPE

## Actos journal advertisement

**GlaxoSmithKline complained about an advertisement for Actos (pioglitazone) placed by Takeda Pharmaceuticals Europe in Diabetologia, April 2008. GlaxoSmithKline supplied Avandia (rosiglitazone). Pioglitazone and rosiglitazone were thiazolidinediones (TZDs).**

**GlaxoSmithKline noted that a previous Actos advertisement, published in January 2008 by Takeda UK had been reviewed by the Medicines and Healthcare products Regulatory Agency (MHRA) and found in breach of the Medicines (Advertising) Regulations. The MHRA was concerned that claims relating to Actos and cardiovascular (CV) risks did not reflect the balance of risks and benefits for the product as stated in the summary of product characteristics (SPC). It was considered that the advertisement was misleading and would not encourage the rational use of Actos. In March 2008 the MHRA asked Takeda UK to provide a corrective statement and not use the advertisement again.**

**GlaxoSmithKline considered that the advertisement now at issue, although different to the one reviewed by the MHRA, was similar.**

**The advertisement in question contained the prominent claim 'There are no long-term cardiovascular concerns regarding the use of Actos (pioglitazone)'. However, there was no mention that Actos was contraindicated in patients with cardiac failure or a history of cardiac failure (NYHA stages I to IV) or might cause fluid retention which might exacerbate or precipitate heart failure and therefore additional monitoring of cardiovascular status might be required in some patients (ref SPC).**

**Given the limited and inadequate presentation of CV data GlaxoSmithKline alleged that the advertisement was not in accordance with the terms of the marketing authorization and was inconsistent with the particulars listed in the SPC; the information provided and the claims were not accurate and did not reflect the balance of risks and benefits as stated in the Actos SPC or contained in the data in their entirety, and were therefore misleading; by presenting inaccurate and misleading data on the CV profile of Actos the advertisement would not encourage the rational use of the medicine. GlaxoSmithKline was particularly concerned that the advertisement could prejudice patient safety, especially as the appropriate checks, required for some patients, were not specifically mentioned within the item.**

**GlaxoSmithKline considered the publication of the advertisement at issue shortly after action taken by the MHRA was an amazing disregard for the very serious points raised by itself and the UK regulatory agency and a breach of Takeda's undertaking to the MHRA. GlaxoSmithKline therefore alleged that Takeda had brought discredit upon, and reduced confidence in, the industry in breach of Clause 2.**

**Diabetologia was published in English in Germany, the editor-in-chief and editorial office was in the UK and it was circulated to UK health professionals as well as to other countries. In the Panel's view promotional material in Diabetologia was subject to the UK Code.**

**The Panel noted that Takeda Europe had placed the advertisement and was taking responsibility under the Code.**

**The Panel noted that the claim 'There are no long-term cardiovascular concerns regarding the use of Actos' appeared as a prominent diagonal highlight band across the top right-hand corner of the advertisement. The Panel considered that this claim was the main message of the advertisement and was put forward as a feature of the product which set it apart from rosiglitazone. The Panel noted however that Section 5.1, Pharmacodynamic properties, of the SPC stated 'Although the study [PROactive, a cardiovascular outcome study] failed to reach 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 the use of pioglitazone. However, the incidences of oedema, weight gain and heart failure were increased. No increase in mortality from heart failure was observed.'**

**Section 4.3, of the SPC stated that pioglitazone was contraindicated in patients with cardiac failure or history of cardiac failure (NYHA stages I to IV). Section 4.4, Special warnings and precautions for use, gave detailed information on fluid retention and cardiac failure stating that pioglitazone could cause fluid retention which might exacerbate or precipitate heart failure.**

**The Panel noted that the advertisement also included the claims that 'Actos… reduces cardiovascular (CV) risk markers', 'Actos is the only thiazolidinedione (TZD) with clinical and safety evidence from a large cardiovascular outcome study in its prescribing information' and 'Results from the CV outcome study, PROactive, confirm**

**there are no long-term CV concerns, such as increased risk of MI, regarding use of Actos…'.**

**The Panel considered that the advertisement sought to minimize prescribers' concerns regarding the CV safety profile of Actos. The claim at issue ('There are no long-term cardiovascular concerns regarding the use of Actos') was not consistent with the SPC which was more qualified regarding the outcome of the study by the use of the phrase 'the results *suggest* [emphasis added] there are no long-term cardiovascular concerns…'. In any event the information in Section 5.1, Pharmacodynamic properties, did not take priority over Sections 4.3, Contraindications, and 4.4, Special warnings and precautions for use. In the Panel's view it was not sufficient to rely on the prescribing information in the advertisement to provide the cautionary note about heart failure. A breach of the Code was ruled.**

**The Panel considered that the advertisement gave the impression there was no need to worry about long-term cardiovascular concerns and this was not necessarily so given that fluid retention caused by pioglitazone might exacerbate or precipitate heart failure and that pioglitazone should be discontinued if any deterioration in cardiac status occurred. The product was contraindicated in patients with, or with a history of, heart failure. The claim at issue was misleading, did not reflect the entire situation and did not encourage the rational use of Actos. Thus the Panel ruled breaches of the Code.**

**With regard to the use of the advertisement after the MHRA had ruled that another advertisement, placed by Takeda UK, was in breach of the advertising regulations, the Panel noted that the final date for copy for the May 2008 edition of Diabetologia was 31 March. The agreed action date between the MHRA and Takeda UK was 5 March. Takeda Europe therefore had time to change the advertisement in Diabetologia. The published report on the MHRA website stated that action had been agreed on 19 March.**

**The Panel noted the MHRA published report that claims relating to pioglitazone did not reflect the balance of risks and benefits as stated in the SPC. The Panel considered that the same point applied to the advertisement in Diabetologia. Given all the circumstances the material should have been amended. In addition the Panel was concerned about the implications for patient safety given its rulings above. Thus the Panel ruled a breach of Clause 2 of the Code.**

GlaxoSmithKline UK Ltd complained about an advertisement (ref ACT179) for Actos (pioglitazone) placed by Takeda Pharmaceuticals Europe Limited in Diabetologia, April 2008. Diabetologia was the journal of the European Association for the Study of Diabetes. GlaxoSmithKline supplied Avandia (rosiglitazone). Pioglitazone and rosiglitazone were thiazolidinediones (TZDs). Inter-company dialogue had not resolved the issues.

## COMPLAINT

GlaxoSmithKline stated that an Actos advertisement (in the style of an advertorial) published in January 2008 by Takeda UK Ltd, in Pulse and GP, was reviewed as part of the Medicine and Healthcare products Regulatory Agency's (MHRA's) scrutiny of published advertising. The MHRA was concerned that claims relating to pioglitazone and cardiovascular (CV) risks did not reflect the balance of risks and benefits for the product as stated in the summary of product characteristics (SPC). It was considered misleading and did not encourage the rational use of the product. The advertisement was found in breach of the Medicines (Advertising) Regulations. The date of action for this breach was 19 March, and the decision was published by the MHRA, on its website, on 3 April. The MHRA asked that Takeda UK Ltd provide a corrective statement regarding the content of the Actos advertisement and directed Takeda that it would not be used again (location and timeline for corrective statement were not provided in the MHRA announcement).

A similar advertisement for Actos was published in Diabetologia on 4 April 2008 and reprinted in the May edition.

GlaxoSmithKline believed this advertisement fell within the scope of the Code as it had clearly been placed by a UK-based company (Takeda Pharmaceuticals Europe Ltd), the journal content was decided upon in the UK (the editor in chief was in the UK) and the UK formed the second largest single European country in terms of journal circulation (information from publisher). The advertisement also had features suggesting that it had been reviewed under the UK Code (inclusion of black triangle, prescribing information and date of preparation of prescribing information).

GlaxoSmithKline discussed its concerns with Takeda UK Ltd but it referred GlaxoSmithKline to Takeda Europe as the advertisement was developed and placed by that company. GlaxoSmithKline had contacted Takeda Europe separately although continued to believe that Takeda UK needed to take responsibility under the Code for the UK audience that had been exposed to the advertisement.

The advertisement in question contained the prominent claim 'There are no long-term cardiovascular concerns regarding the use of Actos (pioglitazone)'. However, there was no mention that Actos was contraindicated in patients with cardiac failure or a history of cardiac failure (NYHA stages I to IV) or might cause fluid retention which might exacerbate or precipitate heart failure and therefore additional monitoring of cardiovascular status might be required in some patients (ref SPC).

Given the limited and inadequate presentation of CV data within the advertisement GlaxoSmithKline believed that:

- The advertisement was not in accordance with

the terms of the marketing authorisation and was inconsistent with the particulars listed in the SPC.
- The information provided and the claims made for pioglitazone were not accurate and did not reflect the balance of risks and benefits for the product as stated in the SPC or contained in the data in their entirety, and were therefore misleading.
- By presenting inaccurate and misleading data on the CV profile of pioglitazone the advertisement would not encourage the rational use of pioglitazone.

GlaxoSmithKline therefore alleged that Takeda UK was in breach of Clauses 3.2, 7.2, 7.9 and 7.10 of the Code.

Given that the advertisement presented inaccurate, incomplete and misleading information about the CV profile of pioglitazone, GlaxoSmithKline was particularly concerned that it might lead to the irrational use of the medicine and could prejudice patient safety, especially as the appropriate checks, required for some patients, were not specifically mentioned within the item.

Importantly, despite the fact that the MHRA provided its view of the advertorial to Takeda on 19 March and GlaxoSmithKline contacted Takeda with its concerns about this advertisement on 18 April, Takeda nevertheless printed the advertisement in Diabetologia in April and again in May. GlaxoSmithKline found this an amazing disregard for the very serious points raised by itself and the UK regulatory agency and a breach of Takeda's undertaking to the MHRA.

GlaxoSmithKline therefore alleged that Takeda had brought discredit upon, and reduced confidence in, the industry in breach of Clause 2.

## RESPONSE

Takeda Europe stated that, contrary to GlaxoSmithKline's view, the Diabetologia advertisement which was the subject of the complaint was very different to the advertorial in Pulse and GP in January 2008. Firstly, the advertorial contained a detailed and discursive presentation of data concerning Actos. In marked contrast, the advertisement now at issue was a short and focussed, up-to-date summary of the Actos SPC, using short bullet points, which closely followed or else exactly reproduced the SPC.

As indicated by the MHRA press release on the previous advertisement, the MHRA considered that the repeated claims about *improved* CV risk were inappropriate in the light of information in the SPC that the product might cause fluid retention, which might exacerbate or precipitate heart failure. The MHRA considered that these positive CV risk claims for improved CV risk for Actos exaggerated the benefits of the product and overshadowed the product's contraindications and the need for ongoing patient monitoring. In its corrective statement Takeda UK accepted that it had got that balance of risks and benefits wrong. Consequently both Takeda UK and Takeda Europe recognised that more prominent statements concerning contraindications and the need for ongoing patient monitoring were appropriate in order to strike the appropriate balance where there was scope for greater discussion of product data.

The focus of the advertisement now at issue was altogether different to that of the advertorial. The advertisement in did not refer to the CV improvement claims like 'protective' or 'improve CV risk', or claim CV risk improvement using the approach developed previously, but rather followed the wording of the SPC. The text was taken from the European SPC, which stated that 'there are no long-term cardiovascular concerns'. This strictly factual approach was altogether different from claiming repeatedly cardio-protection and risk reduction which, the MHRA considered, exaggerated the product's benefits. Takeda Europe considered the information about contraindications and patient monitoring contained in the prescribing information struck an appropriate balance in the advertisement, taking into account its brevity and the low-key, strictly factual approach adopted by virtue of following the SPC. Therefore this advertisement was certainly not 'similar' to the previous advertisement and thus Takeda Europe did not accept that GlaxoSmithKline's references to the MHRA press release were applicable.

Takeda Europe submitted that the copy date for the April edition of Diabetologia was 4 March (before the agreed action date between Takeda UK and the MHRA which was 5 March). The copy date for the May edition was 31 March. Takeda Europe had already informed GlaxoSmithKline that this particular advertising campaign ended with the last advertisement in Diabetologia appearing in the May issue and that there was no intention to re-use the Diabetologia advertisement.

Takeda Europe submitted that Diabetologia was a European publication which had worldwide circulation and was therefore an international journal. Although the journal was published in English, it was not intended solely for the UK market; its largest readership was in Germany where the journal was also produced. Although Takeda Pharmaceuticals Europe had responded to the criticisms by reference to the Code, considering that only 7.4% of its readership was based in the UK, it queried whether the Diabetologia advertisement was in fact subject to the Code.

The claim that 'There are no long-term cardiovascular concerns regarding the use of Actos (pioglitazone)' was taken verbatim from the approved SPC (section 5.1) and therefore could not be stated to be inconsistent with the terms of the marketing authorization or the SPC. In line with Clauses 4.1 and 4.2 of the Code, prescribing information, which included the contraindications

and the additional monitoring requirement referred to by GlaxoSmithKline as well as the other items listed in Clause 4.2 was available on the adjacent page.

The advertisement at issue contained short factual statements about Actos rather than the discursive presentation of the data as in the advertorial in January 2008. This was done with a view to presenting an up-to-date account of the Actos label. However, each bullet point and the diagonal strapline were either taken verbatim from, or else exactly reflected, the SPC. The one exception was the fourth bullet point which referred to the results of the PROactive study – which was of course referenced in the SPC – which simply paraphrased the MHRA's own statement in its 'Drug Safety Update' of December 2007 under the heading 'Myocardial ischaemia' concerning the absence of increased risk of cardiac ischaemia in relation to pioglitazone.

In the absence of any improved CV risk or cardioprotection claims, and taking into account the derivation of each bullet point, Takeda Europe did not accept that the advertisement was not in accordance with the terms of the marketing authorization or that it contained inaccuracies or was misleading or that it failed to encourage the rational use of Actos. After all, it was difficult to see how the company could be more consistent with the SPC than by following it closely and quoting it verbatim.

Since the advertisement promoted Actos within its licence, there was no breach of Clause 3.2.

Since the prescribing information provided clearly stated that Actos could cause fluid retention which might exacerbate or precipitate heart failure and also recommended observation of patients for signs and symptoms of heart failure as well as actions to be taken in case of deterioration of cardiac status (as recommended in the SPC), there was no breach of Clauses 7.2, 7.9 and 7.10. As mentioned above, the company considered that the prescribing information constituted adequate and sufficiently complete information in view of the short format of the advertisement and the factual, closely SPC-oriented approach adopted.

Takeda Pharmaceuticals Europe considered that the advertorial and the advertisement now at issue were both qualitatively and substantively different. Following the concerns raised by the MHRA in relation to the claims made in the advertorial Takeda Europe took care to ensure that no equivalent claims (improved CV risk or cardioprotection) were used in its promotional materials. As the claims in the advertisement closely followed the SPC it believed that the advertisement complied with the Code and was in line with the MHRA's guidance to Takeda UK. Accordingly, Takeda Europe denied a breach of Clause 2.

Takeda Europe was promptly informed by Takeda UK of the MHRA's concerns about the advertorial and took appropriate steps to carefully review all its current promotional materials in the light of the MHRA's comments. As stated above the advertisement did not reproduce the claims which had prompted the MHRA's concerns. Accordingly, Takeda Europe did not accept GlaxoSmithKline's allegations that either company had failed to comply with the requirements for promoting medicines in the UK, whether in a similar fashion to matters raised by the MHRA in connection with the advertorial or otherwise.

## PANEL RULING

Firstly the Panel had to decide whether the advertisement was subject to the Code. Diabetologia (Journal of the European Association for the study of Diabetes (EASD)) was published in English in Germany. The editor-in-chief and editorial office was in the UK and it was circulated to the health professionals in the UK as well as to other countries. In the Panel's view the promotional material published in Diabetologia was subject to the UK Code.

Secondly the Panel had to decide which company was responsible under the Code. The usual arrangement was that the UK company was responsible for activities in the UK even if they were carried out by overseas affiliates/head office etc. However in this instance Takeda Europe had placed the advertisement and was taking responsibility under the Code. In these circumstances the Panel considered that this was acceptable in relation to dealing with the complaint. If however Takeda Europe had not been so minded the matter would have been pursued with Takeda UK.

The Panel noted that the claim 'There are no long-term cardiovascular concerns regarding the use of Actos' appeared as a prominent diagonal highlight band across the top right-hand corner of the advertisement. The Panel considered that this claim was the main message of the advertisement and was put forward as a feature of the product which set it apart from rosiglitazone. The Panel noted however that Section 5.1, Pharmacodynamic properties, of the SPC stated 'Although the study [PROactive, a cardiovascular outcome study] failed to reach 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 the use of pioglitazone. However, the incidences of oedema, weight gain and heart failure were increased. No increase in mortality from heart failure was observed.'

Section 4.3, Contraindications, stated that pioglitazone was contraindicated in patients with cardiac failure or history of cardiac failure (NYHA

stages I to IV). Section 4.4, Special warnings and precautions for use, gave detailed information on fluid retention and cardiac failure stating that pioglitazone could cause fluid retention which might exacerbate or precipitate heart failure.

The Panel noted that the advertisement also included the claims that 'Actos… reduces cardiovascular (CV) risk markers', 'Actos is the only thiazolidinedione (TZD) with clinical and safety evidence from a large cardiovascular outcome study in its prescribing information' and 'Results from the CV outcome study, PROactive, confirm there are no long-term CV concerns, such as increased risk of MI, regarding use of Actos…'.

The Panel considered that the advertisement sought to minimize prescribers' concerns regarding the CV safety profile of Actos. The claim at issue ('There are no long-term cardiovascular concerns regarding the use of Actos') was not consistent with the SPC which was more qualified regarding the outcome of the study by the use of the phrase 'the results *suggest* [emphasis added] there are no long-term cardiovascular concerns…'. In any event the information in Section 5.1, Pharmacodynamic properties, did not take priority over Sections 4.3, Contraindications, and 4.4, Special warnings and precautions for use. In the Panel's view it was not sufficient to rely on the prescribing information in the advertisement to provide the cautionary note about heart failure. A breach of Clause 3.2 was ruled.

The Panel considered that the advertisement gave the impression there was no need to worry about long-term cardiovascular concerns and this was not necessarily so given that fluid retention caused by pioglitazone might exacerbate or precipitate heart failure and that pioglitazone should be discontinued if any deterioration in cardiac status occurred. The product was contraindicated in patients with, or with a history of, heart failure.

The claim at issue was misleading, did not reflect the entire situation and did not encourage the rational use of Actos. Thus the Panel ruled breaches of Clauses 7.2, 7.9 and 7.10.

With regard to the use of the advertisement after the MHRA had ruled that another advertisement, placed by Takeda UK, was in breach of the advertising regulations, the Panel noted that the final date for copy for the May 2008 edition of Diabetologia was 31 March. The agreed action date between the MHRA and Takeda UK was 5 March. Takeda Europe therefore had time to change the advertisement in Diabetologia. The published report on the MHRA website stated that action had been agreed on 19 March.

The Panel noted the MHRA published report that claims relating to pioglitazone did not reflect the balance of risks and benefits as stated in the SPC. The Panel considered that the same point applied to the advertisement in Diabetologia. Given all the circumstances the material should have been amended. In addition the Panel was concerned about the implications for patient safety given its rulings above. Thus the Panel ruled a breach of Clause 2 of the Code which was used as a sign of censure and reserved for such use.

**Complaint received** **7 May 2008**

**Case completed** **29 July 2008**