CASE AUTH/2081/1/08

PRIMARY CARE TRUST PHARMACIST v TEVA

Guidelines in Practice supplement

A pharmacist at a primary care trust (PCT) complained that a supplement sent in association with the electronic edition of Guidelines in Practice and entitled 'Making an informed choice A guide to changing to CFC-free beclometasone inhalers' was disguised promotion for Qvar (CFC-free beclometasone diproprionate (BDP)). The article had been written by a programme director, medicines management, at a PCT. The supplement stated on the front cover that it was supported by an unrestricted educational grant from Teva UK Ltd. Prescribing information for Qvar appeared on the inside back page.

The complainant stated that the title suggested an independent review of the options. The choice of author, a PCT pharmacist, also implied impartiality. However, although some content was good, the complainant found on balance the supplement favoured Qvar more than would be expected from an impartial review. The complainant noted that an 'unrestricted' educational grant from Teva was referred to on the front cover which also directed readers to 'prescribing information' on the inside back page. Only the prescribing information for Qvar was included and not for the alternative product Clenil Modulite.

The Panel noted that the sponsors of the supplement Teva, had commissioned an agency to work with a key opinion leader to create it. The agency had contacted the author. The article was reviewed by Teva and went through its approval process to ensure compliance with the Code. Teva had paid to have copies distributed as a supplement to Guidelines in Practice.

The Panel considered that Teva was inextricably linked to the production of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation of the supplement. Teva's agency and the commissioned author produced the article. The company had paid for it to be distributed. Given the company's involvement the Panel considered that the supplement was, in effect, a paid for insert which promoted Qvar.

The Panel considered that it was disguised promotion in that the insert appeared to be independent of Teva which was not so. The statement on the front cover 'Supported by an unrestricted educational grant from Teva UK Ltd' added to this impression and did not fairly reflect the actual arrangements. A breach of the Code was ruled.

A Primary Care Trust pharmacist complained about a supplement (ref HDM/07/047) sent in association with the electronic edition of Guidelines in Practice and entitled 'Making an informed choice A guide to changing to CFC-free beclometasone inhalers'. The article had been written by a programme director, medicines management, at a PCT. The supplement stated on the front cover that it was supported by an unrestricted educational grant from Teva UK Ltd. Prescribing information for Qvar (CFC-free beclometasone diproprionate (BDP)) appeared on the inside back page.

COMPLAINT

The complainant stated that the title of the supplement suggested an independent review of the options. The choice of author, a PCT pharmacist, also implied impartiality. However, although some content was good, the complainant found on balance the supplement favoured Qvar more than would be expected from an impartial review. The complainant noted that an 'unrestricted' educational grant from Teva was referred to on the front cover which also directed readers to 'prescribing information' on the inside back page. Only prescribing information for Qvar was included and not for the alternative product Clenil Modulite.

The complainant alleged that the supplement was actually an advertisement for Qvar and should not be circulated under the guise of an 'informed' independent prescribing guideline.

When writing to Teva, the Authority asked it to respond in relation to Clause 10.1 of the Code.

RESPONSE

Teva submitted that the article was clearly written by the stated author and not a third party and it complied with the requirements of the Code.

The author, a programme director, medicines management, to a PCT, agreed to write the article and was engaged by Teva's agency. The agency was paid to complete this project, and the fees paid to the author were negotiated directly between the two parties.

Teva had no part in creating the article after agreeing the initial brief. The article was prepared by the author and the agency. At the outset it was agreed that the document would have to go through the Teva approval process for promotional and educational material prior to publication. Throughout the process Teva never communicated directly with the author.

Guidelines in Practice was selected to distribute the article based on an evaluation of its readership for appropriateness of audience and a fee was paid. The editor made some minor suggestions for alterations to the article 'Making an informed choice', which were accepted by the author and reviewed via the Teva approval process. Final approval was granted on 6 September.

Teva submitted that the author chosen by the agency was suitably qualified to write such an article, and was selected as he was an opinion leader who had worked on a transition to CFC-free BDP inhalers and had extensive experience of this subject area. Teva disputed that the title and the choice of the author suggested either an independent review or an impression of impartiality, but rather it suggested an article that discussed the author's opinions and experiences with regard to a guide to changing to CFC-free BDP inhalers.

Teva noted the complainant's comment that 'The choice of author, a PCT pharmacist, also implied impartiality'. Teva considered that this was an emotional comment cleverly used to make the reader believe the article was not impartial but did not provide any data or facts as to why the complainant might believe this to be the case. Teva queried why the complainant considered that the article was not impartial. The company could not understand the comment and requested that if the matter was to be pursued then some detailed reasoning to support this allegation should be provided to enable it to mount a robust defence.

Teva noted that the supplement clearly stated at the outset that it was sponsored by an unrestricted educational grant from Teva. Therefore the opinions expressed in the article were the author's not Teva's.

Teva found the complainant's comment that although some content was good, on balance the supplement favoured Qvar more than would be expected from an impartial review most worrying; it appeared to suggest that the complainant had neither analysed the article in detail nor had the required knowledge to make such a judgement. The article was carefully written using published studies and the author ensured there was equal mention of both Qvar and Clenil where data were available. There were however two sections where Qvar was mentioned and Clenil was omitted. This was not due to bias on the part of the author but simply that Clenil Modulite was only available as a metered dose inhaler (MDI) and did not have any breath actuate inhalers (BAI) in its range of product. Further Trinity-Chiesi had not conducted any studies with Clenil Modulite recording patient reported outcomes such as quality of life and the occurrence of symptom-free days and therefore the product was not discussed in these sections apart from stating that no studies had been conducted.

Teva analysed the content of the supplement and noted the following:

Page 1 (title page): There was no mention of either product

Page 2: There was equal mention of both products

In a table of data it was clearly stated that Qvar was licensed for patients aged 12 years and over and Clenil Modulite was licensed for adults and children, but that patients under the age of 15 years required a volumatic spacer.

Page 3: A comparison of the two products was a fair and accurate reflection of both summaries of product characteristics (SPCs).

Page 3/4: A section regarding delivery devices discussed the benefits of BAIs compared with MDIs and the role of patient compliance. This section related to device and did not discuss either Qvar or Clenil in detail.

Page 4: A discussion of the different particle sizes of medicines was fully referenced and thus was accurate and complied with the Code.

Page 5 (clinical trial evidence): This section was divided into 2 parts which were clearly identified to discuss, in detail, clinical trial evidence of both Qvar and Clenil Modulite; the section relating to Clenil was substantially longer than the Qvar section (46 lines of text vs 35).

Each of these sections reviewed all published studies. In the Qvar section three short-term studies were reported (Magnussen 2000, Gross *et al* 1999 and Davies *et al* 1998) which indicated that Qvar had similar efficacy to CFC-BDP and these were clearly identified as short-term studies. This was followed by a more detailed discussion of the 12 month study (Fireman *et al* 2001) in which patients, who had stable asthma for one month were randomized to receive Qvar or CFC-BDP. The results were accurately depicted and it was clearly stated that there was no difference in peak expiratory flow rate or forced expiratory volume in one second between the groups but as the patients had stable asthma at entry a difference would not be expected. The study utilised a 3:1 randomisation to ensure that a large cohort of patients received Qvar.

The results from the study were also analysed by Price *et al* (2002) and these demonstrated a highly statistically significant difference in the number of symptom-free days between the groups (p=0.006). Teva noted that Price *et al*, as described in the article, used the data generated from the 12-month study for this analysis and did not conduct a separate 12 month study.

The Clenil Modulite section reported five clinical studies that were identified by literature search, four in adults and one in children. The studies lasted either 6 or 12 weeks; there were no studies of a longer duration.

Page 6 (quality of life): This section started by indicating that no studies had been conducted with Clenil Modulite so it clearly stated to the reader that no data were available for which a comparison could be made. The section then discussed Juniper *et al* (2002) in which the quality of life assessment (AQLQ) was reported over a 12 month period. This study was accurately reported indicating that the 'mean AQLQ score improved at each time point' and there was statistically significant improvement at 12 months.

The difference was marked between the two treatments and often there was some confusion as to how the results should be interpreted, but this was clearly described by the authors. The treatment difference between the two study populations was 0.24 and many commentators suggested that this was below the threshold of significance of 0.5. This was an incorrect interpretation of the results because the AQLQ was developed by Juniper and the threshold of 0.5 referred to the clinically meaningful change in any individual and could not be applied to an overall population. Juniper *et al* clearly stated that 'However to reject these results as being clinically unimportant would be erroneous, since the difference of 0.24 only represents the difference between mean values and does not take into account the heterogeneity of patient's response to the interventions'. This was appropriately referenced and as many patients had changed in excess of 0.5 a number needed to treat of between 7-8 was calculated which compared favourably with single digit changes between salmeterol and salbutamol. Indeed Juniper *et al* stated that 20-30% of patients admitted into the study had AQLQ scores of >6 on the 7 point scale and therefore had little ability to improve as the trial progressed. The authors' view that these changes were clinically meaningful was reinforced in the title of the article which Teva noted was published in a peer reviewed journal and the independent referees and the editorial board of the journal must also have agreed with the title 'Clinically important improvements in asthma-specific quality of life, but no difference in conventional indexes in patients changed from conventional BDP to approximately half the dose of extrafine BDP'.

When interpreting results it was important that they were taken in context and Juniper *et al*, when discussing the above results clearly stated that an earlier study that was conducted in just over 100 patients and for a period of 3 months only demonstrated a trend in favour of improved AQLQ results with extrafine BDP but noted that this did not reach statistical significance.

The 12 week study of Juniper *et al* (1999) was also cited in the article at issue.

Page 6/7/8 (changing to CFC-free inhalers): This detailed section discussed the roles of Qvar and Clenil equally and was fully referenced. The discussions were prefaced by a section indicating the measures that might be required such as extra-clinics and asthma reviews followed by an algorithm that in the opinion of the author provided rational decision making process map. Where it was possible to choose Clenil Modulite or Qvar both were mentioned but in situations where a BAI was needed the device that could be considered was mentioned and in some cases this was Qvar Easi-Breathe or Qvar Autohaler.

Teva submitted that manuscripts were selected for inclusion using standard selection criteria for writing a medical review article. It was usual practice to select manuscripts for inclusion that provided a definitive answer but it was not possible to add published references owing to the large numbers of publications in the field of asthma.

Teva submitted that it had demonstrated from the above that the supplement at issue was fair and balanced and thus complied with the Code. If the reader took from the articles that there were benefits in favour of Qvar compared with Clenil then that was only because long-term clinical studies had indeed shown clinical benefit for patients receiving Qvar compared with CFC-BDP but no such comparison could be made with Clenil Modulite as no long-term studies had been conducted.

Teva submitted that the complainant's comment that they expected to see the prescribing information for Clenil Modulite, as well as that of Qvar, indicated that the complainant was unaware of the UK regulations where the sponsoring company should provide prescribing information for its own product but there was no requirement to contain prescribing information from a competitor company. Indeed if this was the case then all articles would need approval from competitors to proceed as the prescribing information was the copyright of the company and all uses would need prior approval as well as sign off against the Code and the SPC in the public domain might not be the latest version. Teva therefore submitted that this was an erroneous suggestion; it did not believe that prescribing information for Clenil Modulite should appear on a supplement sponsored with an unrestricted educational grant from Teva.

Teva noted that Clause 10.1 stated Promotional material and activities must not be disguised. The complainant acknowledged that the front page of the supplement clearly stated that the supplement was supported by an unrestricted educational grant from Teva. The sponsorship was therefore not disguised in any way. The supplementary information to Clause 10.1 stated when a company pays for, or otherwise secures or arranged the publication of promotional material in journals, such material must not resemble editorial matter. The supplement clearly stated the author of the material; the fact that it was a supplement produced in association with Guidelines in Practice and did not refer to it being editorial comment.

Teva further noted as recognized by the complainant, that it was stated that prescribing information could be found on the inside back page. This was included as the material had been through the Teva regulatory approval process as previously stated as was necessary with promotional material under the Code – subsequent to the supplement being written by the

author and edited by the editor of Guidelines in Practice.

In addition, the supplementary information to Clause 10.1 stated 'Sponsorship must be declared in accordance with Clause 9.10' and Clause 9.10 stated 'The declaration of sponsorship must be sufficiently prominent to ensure that readers of the sponsored material are aware of it at the outset'. Teva reiterated that the declaration of sponsorship was on the first page, and the complainant was certainly aware that this piece was sponsored by Teva UK Ltd.

With regard to the complainant's point about the inclusion of the prescribing information of Qvar and not Clenil Modulite, the Code did not call for another company's prescribing information to be provided.

Teva refuted the complainant's allegation that the supplement was 'circulated under the guise of an informed independent prescribing guideline' as the supplement clearly stated the author, the sponsor and did not refer to it being an 'independent prescribing guideline'. The supplement clearly stated that it was an article produced in association with Guidelines in Practice and written by the author. The disclaimer on the back page clearly stated The supplement has been supported by an educational grant from Teva UK Ltd. The views and opinions of contributors expressed in this publication are not necessarily those of Teva UK Ltd, the agency or of Guidelines in Practice, its publisher, advisers and advertisers. In addition, the supplement carried a job code number and a date of preparation, in line with the Code for materials that had been through Teva'a approval process.

In conclusion, Teva considered that it had complied with Clause 10.1 of the Code and that the allegations regarding bias in favour Qvar were unfounded as each section of the publication referred to Qvar and Clenil Modulite in a fair and balanced manner.

PANEL RULING

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided, in relation to material aimed at health professionals, that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its content, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes.

The supplement in question had been sponsored by Teva; the company had commissioned an agency to work with a key opinion leader to create the article. The agency had contacted the author. The article was reviewed by Teva and went through its approval process to ensure compliance with the Code. Copies were distributed as a supplement to Guidelines in Practice for which Teva had paid a fee.

The Panel considered that Teva was inextricably linked to the production of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation of the supplement. Teva's agency and the commissioned author produced the article. The company had paid for it to be distributed. Given the company's involvement the Panel considered that the supplement was, in effect, a paid for insert which promoted Qvar.

The Panel considered that it was disguised promotion in that the insert appeared to be independent of Teva which was not so. The statement on the front cover 'Supported by an unrestricted educational grant from Teva UK Ltd' added to this impression and did not fairly reflect the actual arrangements. A breach of Clause 10.1 was ruled.

Complaint received	**18 January 2008**
Case completed	**21 February 2008**