CASE AUTH/2060/10/07

GENERAL PRACTITIONER v TEVA

Guidelines in Practice insert

A general practitioner complained about an insert distributed with the September issue 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 primary care trust (PCT). The insert 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 dipropionate (BDP)) appeared the inside back page.

The complainant initially thought that the insert was a balanced account of treatment options; that it was 'Supported by an unrestricted educational grant …' and aimed to help health professionals decide which of Qvar and Clenil Modulite (Trinity-Chiesi Ltd's CFC-free BDP) were suitable for patients, supported this view. However, after looking into the supporting evidence in some detail the complainant alleged that the information was not balanced, fair and accurate. The article was potentially misleading and biased.

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 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 and in addition it was being used by the representatives for a promotional purpose. Given the company's involvement, and use of it, the Panel considered that the supplement was, in effect, a paid for insert which promoted Qvar.

The complainant noted that favourable plasma cortisol results for Qvar were discussed from just one of three referenced short term studies (Davies *et al* 1998) without discussing the much less favourable results from Gross *et al* 1999.

The Panel noted that Gross *et al* provided data about plasma cortisol levels. At week 12, 96% or more of patients with run in, end of steroid and end of study values had normal cortisol levels. At week 12 the mean percentage change in plasma cortisol from run in was 9.7% (HFA-BDP) 0.1% (CFC-BDP) and 1.9% (HFA-placebo). No clinically meaningful change in clinical chemistry or vital signs were reported in any treatment group at the end of the 12 week treatment period.

The Qvar Summary of Products Characteristics (SPC) (Section 4.4) stated that BDP and its metabolites might exert detectable suppression of adrenal function. Within the dose range 100-800 micrograms daily, clinical studies with Qvar aerosol had demonstrated mean values for adrenal function and responsiveness within the normal range. However, systemic effects of inhaled corticosteroids might occur, particularly at high doses prescribed for prolonged periods. These effects were much less likely to occur than with oral corticosteroids.

There appeared to be an error in Davies *et al*. The abstract at the start of the paper stated that 'Fewer patients on HFA-BDP than on CFC-BDP had plasma cortisol levels below the normal reference range after 12 weeks of therapy (5.1% vs 17.3% respectively)'. These were the figures cited in the insert in question. The results section of Davies *et al*, however, stated that mean plasma cortisol levels were comparable between the two treatment groups at the end of the run-in period, after oral steroid treatment and at the end of the study. However amongst patients with both a run-in and end-of-study plasma cortisol measure more of those treated with CFC-BDP were found to have plasma cortisol levels below the normal reference range and this difference was statistically significant. Readers were referred to a figure which depicted results of just over 5% for HFA-BDP, and just under 15% for CFC-BDP. The figures given in the discussion section of Davies *et al* were 4.35% for HFA-BDP and 14.43% for CFC-BDP. It thus appeared that the figures of 5.1% and 17.3%, as quoted in the abstract, were incorrect.

The Panel considered that in a section headed 'Clinical trial evidence' it was misleading, regardless of the accuracy of the figures cited in the insert from Davies *et al*, to only refer to plasma cortisol data from that study when relevant data had also been published by Gross *et al*. A breach of the Code was ruled.

The complainant noted that emphasis was placed on

a large long-term study (Fireman *et al* 2001) with favourable results for Qvar, however the article failed to mention that it was open labelled. The complainant thought this was important information especially as the short-term studies were randomised, blinded studies.

The Panel noted Teva's submission about the classification of studies as open-label or blinded. The Panel considered that given the amount and nature of other information included about Fireman *et al* it would have been helpful if it had been made clear that this was an open label study. However, on balance the Panel did not consider it was necessarily a breach of the Code not to mention this and ruled no breach.

The complainant noted that the insert discussed the finding of 'higher percentage of symptom-free days' from a long-term study (Price *et al* 2002) without discussing the contrasting results of symptom-free days from Gross *et al*.

The Panel noted that Price *et al* was of a pharmacoeconomic study and queried whether it should be included in a section headed 'Clinical trial evidence'. It also noted a claim regarding comparing symptom-free days from Price *et al* had already been ruled in breach of the Code (Case AUTH/2007/5/07).

The Panel considered that in a section headed 'Clinical trial evidence' it was misleading to omit the Gross *et al* data on symptom-free days. The studies were of different designs, and Gross *et al* included little detail of the symptom-free data but nevertheless stated that 'The number of symptom-free days and nights and β-agonist use were also equivalent in the two active treatment groups' (HFA-BDP and CFC-BDP). A breach of the Code was ruled.

The complainant noted a section of the insert discussed the favourable quality of life results for Qvar (Juniper *et al* 2002). Again, the open labelled design of the study was not stated. Furthermore, less favourable results from Juniper and Buist, (1999) were not discussed.

The Panel noted that the section on quality of life cited Fireman *et al*, Juniper *et al* and Price *et al*.

Juniper *et al* (based on Fireman *et al* data) stated that although the mean improvement in overall quality of life score over 12 months was greater with HFA-BDP (0.34) than with CFC-BDP group (0.10) the difference between the two was less than the minimal important difference of 0.5. This was not mentioned in the article. Juniper *et al* also determined the proportion of patients for whom quality of life had improved, been maintained or deteriorated. There was a greater proportion of patients for whom quality of life had improved and it was this data that was referred to in the insert. A bar chart presented data from Price *et al* based on Fireman *et al*.

Juniper *et al* referred to Juniper and Buist (a twelve week study) which showed a trend to improved quality of life in the HFA-BDP group compared with the CFC-BDP group. It was possible that the benefit was only achieved after long-term therapy. Further studies were needed to explore the time course in greater depth.

The Panel considered that given the title of the article 'Making an informed choice…',it was misleading not to include details of Juniper and Buist in the quality of life section as alleged. Readers would not have appreciated that benefits in terms of quality of life with Qvar might only be achieved after long-term therapy. The Panel ruled a breach of the Code.

The complainant noted that the concluding statement on quality of life was referenced to Juniper *et al* and Juniper and Buist. Juniper and Buist appeared not to support this statement.

The Panel noted that the statement at issue 'There are also data to show improved QoL [quality of life] for patients treated with Qvar over CFC-containing BDP products[28, 37]', was incorrectly referenced. Reference 28 was Juniper *et al* and there was no reference 37 cited. Reference 36 was Juniper and Buist.

The Panel considered its comments about the quality of life data above. It considered that the claim was too general given the data from Juniper and Buist and Juniper *et al*. It thus ruled breaches of the Code.

The complainant alleged that this section implied that a nurse service was provided to a named PCT by Teva. The Code required that services should be referred to in a non-promotional context.

The Panel noted that the the insert referred to an independent service provided by a pharmaceutical company that included nurses who ran extra asthma review sessions. The insert did not link Teva to the service and the service to the PCT was provided by another company in 2000.

In the circumstances the Panel decided there was no breach of the Code.

The complainant noted that the MHRA was specifically mentioned five times in the insert and this might create a perception that the insert was so endorsed.

The Panel did not consider that mention of the MHRA in the insert created the perception that the insert was endorsed by it.

The Panel noted that the Code prohibited reference in promotional material to inter alia the MHRA. The only exemption to this prohibition was if such reference was specifically required by the licensing authority.

The Panel noted Teva's submission that it had been asked by the MHRA to communicate the MHRA guidance that CFC-free BDP should be prescribed by brand name. It did not appear, however that the MHRA had specifically required Teva to refer to the Agency in its promotional material. Even with the agency's acceptance of the use of its name in promotional material, given the wording of the Code it would nonetheless be unacceptable to mention the MHRA in promotional material unless specifically required by the Agency to do so. The Agency's permission or acceptance could not override the requirements of the Code. The Panel therefore ruled a breach of the Code.

A general practitioner complained about an insert (ref HDM/07/047) distributed with the September issue of Guidelines in Practice entitled 'Making an informed choice. A guide to changing to CFC-free beclometasone inhalers' and written by the programme director, medicines management, at a primary care trust (PCT). The insert 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 dipropionate (BDP)) appeared on the inside back cover.

General comments

Complainant The complainant stated that initially he thought that the insert was a balanced account of treatment options and the statement 'Supported by an unrestricted educational grant …' together with the stated aims to help health professionals decide which of Qvar and Clenil Modulite (Trinity-Chiesi Ltd's CFC-free BDP) were suitable for patients, supported this view.

He had since looked into the supporting evidence and was concerned that the information provided was not balanced, fair or accurate. He queried what action could be taken to ensure that other colleagues who had received this article were made aware of the potentially misleading and biased content.

When writing to Teva, the Authority initially asked it to respond in relation to Clauses 7.2, 7.4 of the Code and subsequently to Clause 9.5 in addition to Clause 18 cited by the complainant.

Respondent Teva believed that the author had produced a balanced and fair review of the material available. When preparing any scientific manuscript the author had to decide what information to include. The article provided an extensive review of the literature and included 36 references of which 23 were published scientific manuscripts. The topic covered was very large and it was normal practice to refer less to old studies when they had been superseded by newer ones. This practice was followed in this article. The complainant seemed to suggest that older studies somehow invalidated the newer references chosen by the author.

Teva noted that the issues raised were identical to those of previous extensive inter-company dialogue with another company; Teva had already successfully answered these issues.

Teva was also concerned that the complainant seemed not to have read or fully understood the studies he had quoted, as they did not support his views. This was very regrettable and had resulted in an ill informed or misplaced complaint.

Teva believed the article was factually correct, fair and balanced. A statement from the author was provided who stood by its content.

Teva reviewed the items raised by the Authority but as requested it had only referred to items that were covered by Clauses 7.2 and 7.4. If the Panel considered that there were any issues that Teva had failed to address, Teva requested that it was informed accordingly.

Making an informed choice (background)

Market research in 2006 demonstrated that health professionals had a poor understanding of the differences between products containing beclometasone for inhalation with the two different propellant agents: (hydrofluoroalkane (HFA) and chlorofluorocarbon (CFC)) and the issues surrounding their use. This situation had been exacerbated by GlaxoSmithKline's announcement that Becotide/Becloforte would be discontinued by October 2007. Currently there was a recognised lack of direction and advice for PCTs from the Department of Health (DoH).

When large numbers of patients required changes in therapy due to product discontinuations medical education programmes assumed a greater importance. As was standard and commonplace in the pharmaceutical industry, Teva commissioned a communications company to work with a key opinion leader to write an independent article. The aim was to provide PCT decision makers and health professionals with a comprehensive review of the clinical data on the CFC and HFA containing BDP preparations, along with advice on how to manage the transition to CFC-free alternatives.

A Programme Director, Medicines Management, at a PCT agreed to be the author of this article and was engaged by the 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 the creation of the article after agreeing the initial brief. The article was prepared by both the author and the agency. At the outset agreements were put in place and it was clearly stated by Teva that the document would have to go through the Teva approval process for promotional and educational material prior to publication.

At a review meeting to ensure that the content of the article would not contravene the Code, Teva was represented by the brand manager (as project

sponsor), its medical director and its medical information manager. A director of the agency was present as project manager and point of communication to the author. 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 by Teva. Final approval was granted on 6 September. Twenty one thousand copies were mailed as a supplement to the Guidelines in Practice, September 2007 edition. A further five thousand copies were supplied to Teva to be used by its field force to provide an independent resource to customers (briefing document provided). The initial feedback from health professionals was that it was well received.

Teva was disappointed that the complainant alleged that the supplement was not balanced, fair and accurate. Teva would demonstrate that this article complied with the Code.

Panel 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; it had been initiated by the company and Teva 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. 21,000 copies were distributed as a supplement to Guidelines in Practice for which Teva had paid a fee; a further 5,000 were supplied to Teva's sales force. The sales force was instructed to use the article proactively in every call where it was appropriate to discuss CFC-free BDP options available to prescribers.

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 and in addition it was being used by the representatives for a promotional purpose. Given the company's involvement, and use of it, the Panel considered that the supplement was, in effect, a paid for insert which promoted Qvar. The Panel then went on to consider the allegations as follows.

1 Clinical trial evidence – plasma cortisol

COMPLAINT

The complainant noted that favourable plasma cortisol results for Qvar were discussed from just one of three referenced short term studies (Davies *et al* 1998) without discussing the much less favourable cortisol results from other studies (Gross *et al* 1999).

RESPONSE

Teva stated that the complainant appeared to have misread the insert as it did not state that all three studies measured the plasma cortisol concentration. The three studies [Gross *et al*, Davies *et al*, and Magnussen 2000] were discussed in term of clinical efficacy and then individual studies were reviewed according to the data they presented. These studies were only mentioned briefly as they were old studies and their results had been superseded by the publication of newer studies in much larger groups of patients, which were conducted over a 12 month period and not a short 10-12 week period.

Gross *et al* and Davies *et al* treated patients with oral steroids (30mg prednisolone) for 7-12 days at the beginning of the study period. Despite these shortcomings there were several important facts that should be considered when comparing outcomes.

- Of the three studies, Magnussen did not measure plasma cortisol concentrations so no comment could be made.

- Gross *et al* measured plasma cortisol concentrations at the end of the run-in period, following a short course of oral prednisolone and after randomised inhaled therapy. No data were presented in the manuscript but the authors stated that 'no clinically meaningful changes in clinical chemistry or vital signs were reported in any treatment group at the end of the 12-week treatment period'. In view of this the author of the insert did not include any results as no data were presented in the manuscript and no clinically meaningful changes were reported.

The insert correctly listed results as they appeared in Davies *et al*. Teva noted that in Davies *et al*, high doses of both medicines were used; patients were randomly allocated to receive either Qvar 800mcg/day or CFC-BDP 1500mcg/day.

The way the data was presented was in-line with the Qvar summary of product characteristics (SPC) which stated that 'Within the dose range 100-800 micrograms daily, clinical studies with Qvar have demonstrated mean values for adrenal function and responsiveness within the normal range'.

Teva therefore did not believe that the data regarding plasma cortisol levels was misleading as alleged. It had been presented in a factual and balanced manner. The reason that further data was not included was that the data were not presented in the manuscripts and to state that the results from Gross *et al* study 'were less favorable' was simply untrue, as Gross *et al* stated that there were 'no clinically meaningful differences' between the treatment groups with reference to the biochemical analyses. Also any differences in results presented by Gross *et al* and Davies *et al* were entirely as expected owing to the much higher steroid dose used in Davies *et al*. Teva believed that the contents of the paragraph at issue were correct, balanced and clearly stated, and therefore did not breach Clauses 7.2 and 7.4.

PANEL RULING

The Panel noted that Gross *et al* provided data about plasma cortisol levels. At week 12, 96% or more of patients with run in, end of steroid and end of study values had normal cortisol levels. At week 12 the mean percentage change in plasma cortisol from run in was 9.7% (HFA-BDP) 0.1% (CFC-BDP) and 1.9% (HFA-placebo). Following these results Gross *et al* stated that no clinically meaningful change in clinical chemistry or vital signs were reported in any treatment group at the end of the 12 week treatment period.

The Qvar SPC (Section 4.4) stated that BDP and its metabolites might exert detectable suppression of adrenal function. Within the dose range 100-800 micrograms daily, clinical studies with Qvar aerosol had demonstrated mean values for adrenal function and responsiveness within the normal range. However, systemic effects of inhaled corticosteroids might occur, particularly at high doses prescribed for prolonged periods. These effects were much less likely to occur than with oral corticosteroids.

There appeared to be an error in Davies *et al*. The abstract at the start of the paper stated that 'Fewer patients on HFA-BDP than on CFC-BDP had plasma cortisol levels below the normal reference range after 12 weeks of therapy (5.1% vs 17.3% respectively)'. These were the figures cited in the insert in question. The results section of Davies *et al*, however, stated that mean plasma cortisol levels were comparable between the two treatment groups at the end of the run-in period, after oral steroid treatment and at the end of the study. However amongst patients with both a run-in and end-of-study plasma cortisol measure more of those treated with CFC-BDP were found to have plasma cortisol levels below the normal reference range and this difference was statistically significant. Readers were referred to figure 5 which depicted results of just over 5% for HFA-BDP, and just under 15% for CFC-BDP. The figures given in the discussion section of Davies *et al* were 4.35% for HFA-BDP and 14.43% for CFC-BDP. It thus appeared that the figures of 5.1% and 17.3%, as quoted in the abstract, were incorrect.

The Panel considered that in a section headed 'Clinical trial evidence' it was misleading, regardless of the accuracy of the figures cited in the insert from Davies *et al*, to only refer to plasma cortisol data from that study when relevant data had also been published by Gross *et al*. A breach of Clause 7.2 was ruled.

2 Clinical trial evidence – design of studies

COMPLAINT

The complainant noted that emphasis was placed on a large long-term study (Fireman *et al* 2001) with favourable results for Qvar, however the article failed to mention that it was open labelled. The complainant thought this was important information especially as the short-term studies discussed earlier contrasted in trial design, in that that they were randomised, blinded studies.

RESPONSE

Teva stated that the complainant implied that the way in which Fireman *et al* was not blinded was important but did not clearly state why this was relevant and seemed to relate the data to previous short-term studies that were randomised.

Teva stated that the allegation was misleading as the studies to which the complainant referred were not all blinded. Although Gross *et al* claimed that the study was blinded the authors did not state how this could have been achieved as double-dummy design was not deemed to be appropriate. Gross *et al* stated that 'A desire only to expose patients to one propellant in order to adequately assess the potential for inhalation effects means that a double-dummy design was not feasible'. In the 1990s there was a vogue to call a study 'single blinded' if the patient was not told the medicine they were receiving, which by today's standards would be disregarded unless the medicines were in identical canisters with indistinguishable labelling. An appropriate level of blinding was also unlikely to have been achieved because metered dose inhalers for HFA-BDP and CFC-BDP had different attributes as the products were present in solution and suspension respectively and had different shapes of canisters. Therefore, in the absence of any details extreme caution must be exercised in relation to the claim that Gross *et al* was a blinded study; by today's standards it would be probably classed as an open-label study, as was Fireman *et al* Price *et al* (2002).

Both Gross *et al* and Fireman *et al* made the same statement regarding the use of double-dummy techniques to blind the study and as both groups agreed and published their articles in well-respected peer review journals, it appeared appropriate to follow their lead. This, however, directly conflicted with the complainant's views but as he provided no reasoning Teva could not comment further. One possible explanation for this difference could be that the complainant had not read and analysed the publications appropriately.

In addition, it was now well accepted that when examining patient reported outcomes studies, these should be at least 3-6 months in length, but current consensus was 12 months. The above position was consistent with the European Medicines Evaluation Agency (EMEA) Committee for Medicinal Products for Human Use (January 2006) paper 'Reflection paper on the regulatory guidance for use of health related quality of life (HRQL) measure in the evaluation of medicinal products'. This stated that unless it was a registration study there was no requirement to use double-dummy studies, it was generally regarded as unethical to replace active medication for placebo. According to Fireman *et al*, performing a double-dummy study of 12 months' duration would not be possible due to poor patient compliance over such period and both Fireman *et al* and Gross *et al* agreed that a double-dummy approach would expose patients to additional risk of receiving a second propellant throughout the study without any possible benefit.

Teva believed that the insert included enough information to allow readers to gain a fair and balanced review of the study in question. It was clear that long-term studies post approval were often conducted in an open fashion as it was regarded as unethical to use placebos to permit a double-dummy technique. This would increase the amount of propellant taken by patients and both Gross *et al* (12 week study) and Fireman *et al* (12 month study) agreed with this position.

The apparent concern with taking greater note of old studies would also seem to disregard the current EMEA guidance that patient reported outcomes required studies with a minimum duration of 3-6 months and there was now a tendency to make these 12 months in duration.

Teva therefore submitted that the studies had been correctly described in a manner that did not breach Clauses 7.2 and 7.4.

PANEL RULING

The Panel noted Teva's submission about the classification of studies as open-label or blinded. The Panel considered that given the amount and nature of other information included about Fireman *et al* it would have been helpful if it had been made clear that this was an open label study. However, on balance the Panel did not consider it was necessarily a breach of the Code not to mention this and ruled no breach of Clause 7.2.

3 Clinical trial evidence – symptom free days

COMPLAINT

The complainant noted that the insert discussed the finding of 'higher percentage of symptom-free days' from a long-term study (Price *et al*) without discussing the contrasting results of symptom-free days from Gross *et al*.

RESPONSE

Teva was surprised at this allegation because Gross *et al* and Price *et al* were different studies and simply not comparable. When a clinical study was compared with another it was important to review and compare all of the relevant criteria which for a trial in asthma should include: study selection, objectives, sample size(s), study design and study medication, duration of the study and patient type (inclusion and exclusion criteria). Studies could only be compared if they were comparable in the above evaluations and in this case it was clear that this was not so.

Study selection

In the case of the studies mentioned by the complainant, only two studies had measured symptom-free days; Gross *et al* and Fireman *et al*/Price *et al*. Gross *et al* conducted a small study of 12 weeks' duration and Fireman *et al* presented the efficacy and safety analysis from a 12 month study and Price *et al* presented an analysis of symptom-free days from the same study.

Gross *et al* claimed that there were no differences in symptom-free days between the treatment groups but no supporting data were presented. In the absence of any data indicating symptom-free values and the 95% confidence intervals, this statement must be interpreted with extreme caution. Conversely Fireman *et al*/Price *et al* presented full data on the median values of symptom-free days and the 95% confidence intervals and as the study was conducted over a 12 month period Teva concluded that the conclusions were robust. The differences in favour of the number of symptom-free days experienced by patients receiving HFA-BDP were highly significant (P=0.006). Teva had discussed this matter with Professor Price and he fully supported this conclusion.

Objectives

The objective of Gross *et al* was to confirm if '[due to] improved lung deposition of [Qvar] in comparison to CFC-BDP…lower doses of [Qvar] may be required to provide adequate asthma control'. The primary endpoint variable was 'morning PEF [peak expiratory flow] over week 1 to 3, 4 to 6, 7 to 9 and 10 to 12'. The groups were analysed 'using an analysis of variance ANOVA with treatment, centre and treatment-by-centre interaction terms'. Asthma symptoms were recorded but no data on symptom-free days were presented in the manuscript.

The objective of Fireman *et al* was to 'evaluate the long-term efficacy and safety of switching patients with asthma maintained on stable dose of CFC-BDP pMDI to therapy with HFA-BDP pMDI at approximately half of their previous dose of CFC-BDP'. There was no primary efficacy variable stated in the manuscript but it was stated that PEF (am and pm), FEV1 (Forced Expiratory Volume over 1 second), daily asthma symptoms and number of times beta agonists were used, were recorded.

The objective of Price *et al* was 'To compare the cost effectiveness of hydrofluoroalkane [Qvar] with [CFC-BDP] in patients with chronic stable asthma previously receiving CFC-BDP, from the perspective of a healthcare provider'. The main outcome measure was 'average and incremental cost-effectiveness ratios based upon symptom-free days, improvement in health-related quality of life, and total drug-only direct healthcare costs'.

Sample size

In Gross *et al*, 113, 117 and 117 patients were enrolled into the three treatment groups of HFA-BDP, CFC-BDP and HFA-placebo respectively.

Fireman *et al*/Price *et al* enrolled 473 patients of which 350 received HFA-BDP and 118 received CFC-BDP. Therefore, Fireman *et al*, as it contained a much larger sample size had a significantly greater statistical power than Gross *et al* so it was not surprising that Firemen *et al* detected differences that were not seen in Gross *et al*.

When evaluating a study it was usual practice to consider whether there was an adequate number of patients enrolled to ensure that any conclusion was robust and could withstand scrutiny. In the 1980/90s many studies provided misleading results because insufficient patients were enrolled and later the conclusions might have to be revised or amended following trials in larger numbers of patients. As a result the required sample size was commonly determined from pilot studies, which although too small to provide a reliable conclusion provided an assessment of the likely difference in outcomes that would be encountered in the subsequent study.

Therefore, when considering whether a result was appropriate and robust enough for application to patient care the sample size and the power of the study must be taken into account.

Design and medication

The two studies had very different study designs, and were not directly comparable. It was therefore inappropriate to combine the results and interpret them in the same way as described in the ruling.

Oral steroids modified the symptoms in asthma and this difference alone could make these studies incomparable. Patients in Gross *et al* study all treated with 30mg oral steroids (prednisolone) for 7-12 days demonstrated reversibility of asthma symptoms as assessed by at least 15% increase in morning PEF rate. In a striking contrast, patients in Fireman *et al*/Price *et al* were not allowed any steroids for 30 days before entry into the study. This was a major difference between the two studies and symptoms assessments for such a large oral steroid dose needed to be reviewed with caution.

As oral steroids were very effective in controlling symptoms and generating a feeling of well-being symptom scores could not be regarded as reliable, especially in the first half of the study. Fireman *et al*/Price *et al* on the other hand assessed symptom-free days over a long period of time (12 months) and patients did not receive a large loading dose of oral steroids at the beginning of the study.

Fireman *et al*/Price *et al* and Gross *et al* had very different study durations.

- Gross *et al* had a 10-12 day run-in period followed by 12 weeks' treatment.
- Fireman *et al*/Price *et al* was conducted over 12 months with no oral steroid run-in period.

In Gross *et al* patients were randomised to receive either HFA-BDP at 400mcg/day or CFC-BDP 800mcg/day following the 7-12 days on oral steroid therapy. This medication schedule was biased in favour of the CFC-BDP and the patients had uncontrolled asthma as defined by the fact that the patients had to experience symptoms in the last 5 days of the run-in period. The dose of HFA-BDP was lower than that licensed for use in the UK as indicated by the Qvar SPC which stated that a 2:1 dose ratio of Qvar to CFC-BDP was licensed for use in controlled patients and in patients with uncontrolled asthma the dose of Qvar should be 1:1 compared with CFC-BDP.

This was a major confounding factor in this study design and medication selection. Conversely Fireman *et al*/Price *et al* only admitted patients who had controlled asthma symptoms over the month prior to entry and thus the selection of the dose of 400mcg/day of Qvar was appropriate and in-line with the UK SPC.

Patient type

Another major fundamental difference between these studies was the choice of patients. While the two studies were conducted in patients with asthma, patients in each study differed significantly in degree of the control of symptoms before enrolment. These differences alone might eliminate any short-term therapy benefits.

In Gross *et al* patients had 'at least moderately severe asthma' and 'were required to show signs and symptoms of acute asthma during the last 5 days of run-in [period]'. Gross *et al* defined asthma symptoms as a mean morning PEF between 50% and 80% of predicted normal value plus one of the following: Sleep disturbance on ≥1 nights; asthma symptoms on ≥3 days or use of a beta-agonist inhaler on average twice daily to relieve symptoms.

In Fireman *et al*: 'patients aged ≥12 years with at least 6-month history of asthma (and stable symptoms for the past month) were enrolled'.

The patient populations were therefore not comparable in many ways. This was an important difference between the study populations and there was now general acceptance that studies were required to reflect the real life setting rather than using highly selected patient populations. Herland *et*

al (2005) estimated that if patients were highly selected by the entry criteria as few as 1.3% of patients with asthma would be eligible to enter into the study.

In conclusion Teva submitted that the studies were very different in design and execution and were not comparable. There were major differences in:

- patient types: Gross *et al* studied uncontrolled asthma patients and Fireman *et al*/Price *et al* studied patients with stable symptoms for the last month prior to entry.

- dosing regimens; Gross *et al* used a large prednisolone dose of 30mg/day prior to randomisation of study.

- periods of time: Fireman *et al*/Price *et al* followed patients for 12 months whilst Gross *et al* was only a 12 week study period which was too short to detect meaningful differences in symptom-free days. Only the 12 month study had enough patients and hence power to detect a statistically significant difference in symptom-free days.

In view of these differences between the studies and the fact that the results were accurately presented in the insert Teva did not understand why the complainant was concerned and it submitted that this paragraph did not contravene Clauses 7.2 and 7.4.

PANEL RULING

The Panel noted that Price *et al* was of a pharmacoeconomic study and queried whether it should be included in a section headed 'Clinical trial evidence'. It also noted a claim comparing symptom-free days from Price *et al* had already been ruled in breach of the Code in Case AUTH/2007/5/07.

The Panel considered that in a section headed 'Clinical trial evidence' it was misleading to omit the Gross *et al* data on symptom-free days. The studies were of different designs. It accepted that Gross *et al* included little detail of the symptom-free data but nevertheless stated that 'The number of symptom-free days and nights and β-agonist use were also equivalent in the two active treatment groups' (HFA-BDP and CFC-BDP). The Panel ruled a breach of Clause 7.2.

4 Quality of life

COMPLAINT

The complainant noted that the insert discussed the favourable quality of life results for Qvar (Juniper *et al* 2002). Again, the open labelled design of the study was not stated. Furthermore, less favourable results from Juniper and Buist (1999) were not discussed.

RESPONSE

Teva noted that firstly in the papers cited by the complainant, it was clearly stated that Juniper *et al*, Fireman *et al* and Price *et al*, reported on the dataset from a single study. This was ignored by the complainant. Gross *et al* and Juniper and Buist also reported data from the same study, which was also ignored.

Therefore the first part of the complaint was exactly the same point as raised in Point 3 above. As this question was repeated from the previous paragraph Teva assumed that the complainant had not read the papers in sufficient detail to be aware of the relationship between the studies. Teva therefore referred the question of design and blinding of Gross *et al*, Juniper and Buist vs Juniper *et al*, Fireman *et al* and Price *et al* to its submission in Point 3.

With regard to the second part once again the issue was one of a short-term, underpowered, small study in uncontrolled patients who received oral steroid load compared to a 12 month study in the well controlled patients in a much larger study.

Juniper and Buist was a small study with 113 patients receiving Qvar this was followed by the larger study (Juniper *et al*) with 354 patients receiving Qvar.

Juniper and Buist was described by the complainant as being less favourable than Juniper *et al* which was not the so. The two manuscripts stated:

- Juniper and Buist measured a change in [quality of life] score from baseline and again at the end of the trial, (12 weeks). It was noted that 'The changes in each of the active treatment groups were significantly different from those observed in the placebo group (p 0.003). Although there was a trend in favour of HFA-BDP compared with CFC-BDP, the difference was small and not statistically significant (p=0.29)'.

- Juniper *et al* measured a change from baseline of [quality of life] score at 0, 2, 4, 8 and 12 months. It was noted that 'Improvements from baseline in overall [quality of life] scores were seen for both treatment groups at each time point, but these results were consistently higher for HFA-BDP than CFC-BDP'.

In Juniper *et al* the authors stated 'At month 12, there was a statistically significant difference between treatment groups in change from baseline in overall [quality of life] in favour of HFA-BDP (p= 0.019), which was also seen in the symptom (p=0.041) and emotional function (p=0.025) domains. For the activity limitation domain, the difference between groups at month 12 approached statistical significance (p=0.073)'.

It was therefore noted in both Juniper and Buist (at 3 months) and in Juniper *et al* (at 2 and 4 months) that there was no statistical significance in [quality of life] score change from baseline at these time points. However both trials reported a slightly higher score in favour of HFA-BDP (Qvar) compared to CFC-BDP but the results were highly significant at 12 months.

In conclusion Teva submitted that it was not correct to state that Juniper and Buist demonstrated less favourable results for quality of life when compared to Juniper *et al*. These papers reported consistent results. As the results from Juniper and Buist were consistent with, and superseded by Juniper *et al* which was longer in duration, had a larger sample size and was more recent in publication, the author of the insert did not include the data from Juniper and Buist and Teva agreed with this decision. Notwithstanding the similarity and consistency of results it would also have been inappropriate to combine the studies in the way the complainant suggested as the studies were not comparable in any way as discussed in the previous section.

Teva therefore believed that this section of the insert was well written, fair, factual and not misleading and did not breach either Clause 7.2 or Clause 7.4.

PANEL RULING

The Panel noted that the section on quality of life cited Fireman *et al*, Juniper *et al* and Price *et al*.

Juniper *et al* (based on Fireman *et al* data) stated that although the mean improvement in overall quality of life score over 12 months was greater in the HFA-BDP group (0.34) than in the CFC-BDP group (0.10) the difference between these values (0.24) was less than the minimal important difference of 0.5. This was not mentioned in the article. Juniper *et al* then went on to look at the proportion of patients for whom quality of life had improved, been maintained or deteriorated. There was a greater proportion of patients for whom quality of life had improved and it was this data that was referred to in the insert. A bar chart presented data from Price *et al* based on Fireman *et al*.

Juniper *et al* also mentioned that HFA-BDP patients experienced a significant improvement in the asthma-specific quality of life even when no differences in conventional clinical measurement of lung function was observed. The reason for this difference was not clear. A couple of suggestions were made, these being firstly that HFA-BDP spray was deposited in more peripheral airways and this led to changes in quality of life but were not captured as FEV1 or PEF assessments or secondly the clinical indexes were not sufficiently sensitive to detect changes. Juniper *et al* stated that the lack of correlation was not unexpected as it was a well documented finding which highlighted the need to assess asthma-specific quality of life in clinical trials.

Juniper *et al* referred to Juniper and Buist which showed a trend to improved quality of life in the HFA-BDP group compared with the CFC-BDP group. It was possible that the benefit was only achieved after long-term therapy. Further studies were needed to explore the time course in greater depth.

Juniper and Buist was based on Gross *et al* and concluded that HFA-BDP was as effective as CFC-BDP in sustaining improvements in quality of life following withdrawal of 7 to 12 days of prednisolone. The study lasted 12 weeks and stated that the number needed to treat with HFA-BDP in order for one patient to benefit compared to CFC-BDP treatment was 21.1. (The figure in Juniper *et al* and mentioned in the insert was between 7 and 8.)

The Panel considered that given the title of the article 'Making an informed choice…', it was misleading not to include details of Juniper and Buist in the quality of life section as alleged. Readers would not have appreciated that benefits in terms of quality of life with Qvar might only be achieved after long-term therapy. The Panel ruled a breach of Clause 7.2.

5 Conclusion

COMPLAINT

The complainant noted that the concluding statement on quality of life was referenced to Juniper *et al* and Juniper and Buist. Juniper and Buist appeared not to support this statement.

RESPONSE

Teva submitted that the complainant simply re-iterated the text in Point 4 and this was fully answered.

PANEL RULING

The Panel noted that the statement at issue 'There are also data to show improved QoL [quality of life] for patients treated with Qvar over CFC-containing BDP products[28, 37]', was incorrectly referenced. Reference 28 was Juniper *et al* and there was no reference 37 cited. Reference 36 was Juniper and Buist.

The Panel considered its comments about the quality of life data above. It considered that the claim was too general given the data from Juniper and Buist and Juniper *et al*. It thus ruled breaches of Clauses 7.2 and 7.4.

6 Extra clinics

COMPLAINT

The complainant alleged that the insert implied that a nurse service was provided to a named PCT by Teva.

Clause 18 clearly stated that services should be referred to in a non-promotional context.

RESPONSE

Teva stated that a nurse service was provided to the named PCT in 2000. It was not sponsored by Teva UK Ltd or Ivax. The complainant was incorrect. The insert clearly stated that the nurse service was provided by 'a pharmaceutical company' and not Teva as stated by the complainant.

The provision of this nurse service pre-dated the

acquisition of Qvar by Ivax by several years. Therefore, any complaint should be directed to the company which was the marketing authorization holder at the time. Teva stated that it could not comment further.

PANEL RULING

The Panel noted that the complainant was correct in that the provision of medical and educational goods and services should not be linked to the promotion of a medicine.

The insert referred to an independent service provided by a pharmaceutical company that included nurses who ran extra asthma review sessions. The insert did not link Teva to the service and the service to the named PCT was provided by another company in 2000.

In the circumstances the Panel decided there was no breach of Clause 18.4.

7 Reference to the Medicines and Healthcare products Regulatory Agency (MHRA)

COMPLAINT

The complainant noted that the MHRA was specifically mentioned five times in the insert and this might create a perception that the insert was endorsed by the UK authority.

RESPONSE

Teva refuted this suggestion totally as it was very clear that the statements at issue only related to the MHRA guidance about the prescription of CFC-free BDP by brand. The insert had cited this guidance because, as stated by the MHRA, incorrect prescribing of CFC-free BDP was a major issue relating to patient safety. It was also essential to indicate that this was not a company warning or guideline, which could often be ignored, but instead was an alert from the MHRA which should be followed. If Teva was to make these statements it believed health professionals could ignore the warnings and thus put patient safety at risk. Teva had had several discussions with both the MHRA and DoH which culminated in the MHRA guidance in August 2006. It had been informed that it was appropriate for Teva to communicate this message to health professionals. This was further reinforced to the Teva staff at a meeting on 1 August 2007 attended by the DoH and the MHRA. However in view of the large numbers of complaints Teva had recently received via the Authority it now submitted each item where the guidance was mentioned to the MHRA for approval and in future each item would be appropriately approved.

Teva believed that it was appropriate to ensure that health professionals prescribed CFC-free BDP by brand as recommended by the MHRA and would include these recommendations in all communications.

As this was agreed with the MHRA Teva did not believe that this contravened Clause 9.5 but to ensure that there was no ambiguity it would continue to obtain MHRA approval each time it mentioned and referenced the MHRA guidance.

PANEL RULING

The Panel did not consider that mention of the MHRA in the insert created the perception that the insert was endorsed by it.

The Panel noted that Clause 9.5 prohibited reference in promotional material to inter alia the MHRA. The only exemption to this prohibition was if such reference was specifically required by the licensing authority.

The Panel noted Teva's submission that it had been asked by the MHRA to communicate the MHRA guidance that CFC-free BDP should be prescribed by brand name. It did not appear, however that the MHRA had specifically required Teva to refer to the agency in its promotional material. Even with the agency's acceptance of the use of its name in promotional material, given the wording of Clause 9.5 it would nonetheless be unacceptable to mention the MHRA in promotional material unless specifically required by the agency to do so. The agency's permission or acceptance could not override the requirements of the Code. The Panel therefore ruled a breach of Clause 9.5.

During its consideration of this point the Panel noted that Teva had provided a copy of email correspondence between its agency and the MHRA wherein the MHRA consented to use of its name in a piece of promotional material. The matter had been discussed with the MHRA Director of Communications. The Panel was concerned that there did not appear to be communication with the post-licensing division of the MHRA.

Complaint received	**18 October 2007**
Case completed	**28 January 2008**