CASE AUTH/2007/5/07

TRINITY-CHIESI v TEVA

Qvar leavepiece

Trinity-Chiesi alleged that the claim 'Twice as many symptom-free days' [compared with CFC beclometasone (BDP)] in a leavepiece for Qvar issued by Teva was not a fair and balanced representation of the available published evidence. Qvar was a CFC-free BDP inhaler for asthma. The claim was referenced to Price *et al* (2002). Price *et al* cited Fireman *et al* (2001) as principally responsible for reporting on the clinical and safety aspects of the open label study in question and therefore statements from Fireman *et al* regarding efficacy or safety were considered by Trinity-Chiesi to be important in relation to this study.

Trinity Chiesi alleged that in highlighting Fireman *et al*, Teva had largely ignored three key randomised, double-blind, double dummy studies. For example, Gross *et al* (1999) reported no difference between Qvar and equipotent doses of CFC-BDP when symptom-free days were assessed during the three month study involving 347 asthma patients. Additionally, no difference in the incidence of asthma symptoms was observed between asthma patients treated with Qvar compared with those treated with equipotent does of CFC-BDP in another two similarly designed studies (Magnussen *et al* 2000 and Davies *et al* 1998).

Furthermore, Fireman *et al* reported no significant differences in changes from baseline in the percentage of days without wheeze, shortness of breath or chest tightness throughout the study, whereas there was a statistically significant difference in the percentage of days without cough in favour of Qvar. Importantly, Fireman *et al* stated that although the result was statistically significant, it was probably not clinically significant. Teva had not acknowledged this important point in its material. This unquestionably cast doubt on the clinical significance of the claim.

Finally, assessment of symptom-free days was not stated to be a primary endpoint in Fireman *et al* therefore Trinity Chiesi alleged that only highlighting this data was misleading especially as no differences between Qvar and equipotent doses of CFC-BDP were observed in terms of efficacy and tolerability.

The Panel noted that the claim in question was referenced to Price *et al* which was a pharmacoeconomic study based on the results of Fireman *et al*.

Fireman *et al* examined whether asthmatic patients with symptoms controlled with CFC-BDP could be switched to CFC-free BDP at half the CFC-BDP dose without *inter alia*, adversely affecting the control of asthma symptoms. The authors demonstrated an overall increase in the percentage of symptom-free days (without wheeze, shortness of breath or chest tightness) between baseline and month 12 in the CFC-free BDP group (11.5%) and the CFC-BDP group (4.6%). No significant differences in the change from baseline in percentage of symptom free days were seen throughout the study. There were slight differences between CFC-free BDP and CFC-BDP in percentage of days without cough which although statistically significant at weeks 1 to 2 and at months 7 to 8 were described as probably not clinically significant. During months 7 to 8 patients on CFC-free BDP had a significantly greater proportion of nights without sleep disturbance than patients on CFC-BDP. The study concluded that asthma control was maintained in patients switched from CFC-BDP to CFC-free BDP.

Price *et al* re-examined Fireman *et al* for the cost effectiveness study. Price defined 'symptom-free day' as the absence of all of the following: wheeze, cough, shortness of breath, and chest tightness in one day including overnight. Patients in the CFC-free BDP group had a higher median percentage of symptom-free days than patients in the CFC-BDP group (42.4% v 20%; p=0.006). This equated to three symptom-free days per week in the CFC-free BDP group compared with 1.4 in the CFC-BDP group. The mean data which showed that the percentage of symptom-free days at 12 months was 45.6% (CFC-free BDP) and 35% (CFC-BDP), showed no statistically significant difference between the two treatment groups. This mean data appeared to be that which Fireman *et al* had used to report an increase from baseline of 11.5% (CFC-free BDP) and 4.6% (CFC-BDP) in percentage of days without wheeze, shortness of breath and chest tightness.

The Panel noted that, on a re-examination of the clinical data by Fireman *et al*, Price *et al* had reported statistically significantly more symptom-free days for patients taking CFC-free BDP compared with those taking CFC-BDP. The study authors had used a median percentage. The mean percentage did not show a statistically significant difference. The primary clinical data had not reported such a difference although there was a trend in favour of CFC-free BDP. Other studies (Davies *et al*, Gross *et al* and Magnussen *et al*) although shorter in duration (12 weeks or less) had demonstrated equivalent control of asthma for CFC-free BDP and CFC-BDP. Price *et al* was the only study to report that CFC-free BDP produced 'twice as many symptom-free days' as CFC-BDP. Overall

the Panel did not consider that the data was sufficiently robust to support such a strong claim and in that regard the claim 'Twice as many symptom-free days' was misleading in breach of the Code.

Upon appeal by Teva, the Appeal Board noted that Fireman *et al* evaluated whether asthma patients with symptoms controlled with CFC-BDP could be switched to CFC-free BDP at half the CFC-BDP dose without, *inter alia*, adversely affecting the control of asthma symptoms. The authors recorded that there were no consistent differences between the treatment groups with regard to individual asthma symptoms (wheeze, cough, shortness of breath and chest tightness) or daily use of reliever inhalers. Both groups recorded an increase in percentage of symptom-free days between baseline and one year (CFC-BDP 4.6% vs CFC-free BDP 11.5%). The authors concluded that asthma control was maintained in both groups.

Based on the clinical data generated by Fireman *et al*, Price *et al* compared the cost effectiveness of CFC-free BDP with CFC-BDP. Price *et al* assessed asthma symptoms in terms of symptom-free days which was a composite end point defined as the absence of all of the following: wheeze, cough, shortness of breath and chest tightness, in one day (including overnight). A table of data recorded the percentage symptom-free days and showed at baseline the median percentage symptom-free days in the CFC-free BDP group was 21.4% [95% confidence interval 14.3-28.6] and in the CFC-BDP group it was 12.7% [6.7-28.6] (p=0.226), ie there was almost a two fold difference between the groups at baseline. This difference was maintained throughout the study such that after one year the median percentage symptom-free days in the CFC-free BDP group was 42.4% [32.1 – 57.9] and 20% [3.8 – 37.9] in the CFC-BDP group. The Appeal Board noted that the confidence intervals overlapped. It was this data which formed the basis of the claim 'Twice as many symptom free days'.

The Appeal Board did not consider that Price *et al* was sufficiently robust as to support the claim 'Twice as many symptom free days'. The data had been derived from a pharmacoeconomic evaluation of primary clinical data in which no difference between CFC-free BDP and CFC-BDP in terms of asthma control had been shown. There was no indication that Price *et al* had been powered to detect a statistical difference in percentage symptom-free days; there had, in any case, been a two-fold difference between the two treatment groups at baseline in this regard, a difference which was present at the end of the study. The Appeal Board considered that given the data on which it was based the claim at issue was misleading and upheld the Panel's ruling of a breach of the Code.

Trinity-Chiesi Pharmaceuticals Ltd complained about the promotion of Qvar by Teva UK Limited. Qvar was a CFC-free beclometasone diproprionate (BDP) inhaler for asthma. A number of allegations were made about a number of materials. Each was carefully examined and following protracted correspondence with both parties the Director decided that the only matter upon which the requirements for inter-company discussion in Paragraph 5.2 of the Constitution and Procedure had been met related to a claim 'Twice as many symptom-free days'.

The material at issue was a leavepiece (ref IV/QV/CNL/12/06A and IV/QV/CFC/01/07) stated by Trinity-Chiesi to be recently delivered by a Teva representative to a health professional. Trinity-Chiesi supplied Clenil Modulite and Pulvinal Beclometasone.

COMPLAINT

The claim 'Twice as many symptom-free days' was referenced to Price *et al* (2002). Price *et al* cited Fireman *et al* (2001) as principally responsible for reporting on the clinical and safety aspects of the open label study in question and therefore statements from Fireman *et al* regarding efficacy or safety were considered by Trinity-Chiesi to be important in relation to this single study.

Trinity-Chiesi alleged that the claim 'Twice as many symptom-free days' was not a fair and balanced representation of the available published evidence. Teva had highlighted data from a 12 month randomised, open label trial (Fireman *et al*) and largely ignored the results from three key randomised, double-blind, double dummy studies. For example, Gross *et al* (1999) reported no difference between Qvar and equipotent doses of CFC-BDP when symptom-free days were assessed during the three month study involving 347 asthma patients. Additionally, no difference in the incidence of asthma symptoms was observed between asthma patients treated with Qvar compared with those treated with equipotent does of CFC-BDP in another two similarly designed studies (Magnusson *et al* 2000 and Davies *et al* 1998).

Furthermore, Fireman *et al* reported that no significant differences were observed in changes from baseline in the percentage of days without wheeze, shortness of breath or chest tightness (ie three of the four symptoms) throughout the study, whereas there was a statistically significant difference in the percentage of days without cough in favour of Qvar. Importantly, Fireman *et al* stated that although the result was statistically significant, it was probably not clinically significant. Teva had failed to acknowledge this important point in its material. This unquestionably cast doubt on the clinical significance of the claim.

Finally, assessment of symptom-free days was not stated to be a primary endpoint in Fireman *et al* therefore only highlighting this data in Qvar promotional material was alleged to be misleading especially as no differences between Qvar and equipotent doses of CFC-BDP were observed in terms of lung function parameters (usually primary efficacy endpoints) and tolerability.

In summary, Teva had not discussed any of the other relevant published data mentioned above and had selected data that did not reflect all the available evidence. This was misleading and not balanced, in breach of Clause 7.2 of the Code.

RESPONSE

Teva stated that Trinity-Chiesi was incorrect in its description of Gross *et al* on several accounts:

1 Gross *et al* was not a double-blind double-dummy study which was clearly stated in the 'Methods' and 'Discussion' sections.

2 Patients in Gross *et al* were a different patient population. Patients had uncontrolled asthma symptoms, whilst in the Fireman/Price study the patients' asthma symptoms were stable for one month prior to entry into the study and were simply randomised to receive the study therapies.

3 The number of patients in Gross *et al* that received CFC-free BDP was only 113 patients compared to 354 in the Fireman/Price study. The sample size was so small in Gross *et al* that a difference in symptom-free days would not be expected.

4 Gross *et al* was a very short-term study of only 12 weeks and to demonstrate an increase in symptom-free days between therapies a longer study period was required. This was why a 12-month study was conducted several years later and a positive result was demonstrated owing to the appropriate study period of 12 months' duration.

The other two papers quoted by Trinity-Chiesi, Magnussen *et al* and Davies *et al* also were of small sample size, short duration (12 weeks), were in widely differing patient groups and used variable doses. These used different criteria for patients enrolled, and different study conditions to those reported in Fireman/Price. The differences compared to Fireman/Price were;

1 Davies *et al* enrolled patients with moderately severe uncontrolled asthma symptoms and delivered doses of 800mcg day CFC-free BDP and 1500mcg/day CFC-BDP over a 12-week study period.

2 Gross *et al* enrolled patients with uncontrolled asthma symptoms and delivered doses of 400mcg/day CFC-free BDP and 800mcg/day of CFC-BDP over a 12-week study period.

3 Magnussen *et al* although enrolled patients with stable moderate asthma did not use equipotent doses as stated by Trinity-Chiesi but used higher CFC-doses which would militate against demonstrating a benefit in favour of CFC-free BDP. The study delivered doses of 400mcg/day CFC-free BDP and 1000mcg/day of CFC-BDP for a 10-week period.

Teva submitted that it was quite clear that none of the three studies quoted were directly comparable to the data from Fireman/Price and were therefore irrelevant to the interpretation of Fireman/Price. This point had been made several times to Trinity-Chiesi but had been ignored.

In addition Teva believed that the comments relating to its ability to support the claim with Price *et al* were erroneous as Trinity-Chiesi had ignored the central hypothesis as declared by the authors. It was rather difficult to understand that Trinity-Chiesi would not accept conclusions from a study published by leading experts in the field that had been vetted and agreed by the journal referees and had been deemed to be correct and worthy of publication by a prestigious journal that was well respected and widely read.

1 The hypothesis tested was directly linked to the study design and methodology employed, this in turn was directly linked to the results and any subsequent promotional claims for a product had been referenced to appropriate clinical studies.

2 In Price *et al* the concept of symptom-free days was based on improving the patients' ability to lead a normal life. The National Asthma Education and Prevention Program in the USA recommended the measure 'symptom-free day' as the principle outcome measure for cost-effectiveness analysis of asthma interventions. This was recognised in the forthcoming National Institute for Health and Clinical Excellence (NICE) review on inhaled corticosteroids (ICS) and long acting beta agonists (LABA) for the treatment of chronic asthma in adults and children 12 years and over: systematic review and economic analysis. The General Practice Airways Group also noted that 'Much of the analysis is based on studies with endpoints that have little meaning in the day to day asthma clinic; this is a particular problem where an economic analysis is attempted. Randomised clinical trials have traditionally been carried out on patients who have to fulfil very strict criteria drawn from secondary care and who do not represent the bulk of asthma patients seen in primary care.'

Teva disputed Trinity Trinity-Chiesi submission that Fireman *et al* was important in relation to safety and efficacy, as the hypothesis of the study was the 'Evaluation of the long term (12 months) efficacy and safety of switching patients with asthma maintained on a stable dose of CFC-BDP pMDI to therapy with [CFC-free BDP] at approximately half their previous daily dose of CFC-BDP'. Teva however disputed that this study should be used in relation to a promotional claim based on symptom-free days, as it clearly did not investigate symptom-free days as a primary end point nor did it provide statistical analysis of symptom-free days. All claims relating to symptom-free days were referenced to the more detailed analysis (pharmacoenconomics) conducted by Price *et al*.

Teva summarized Price *et al* as follows: The objective was to compare the cost effectiveness of CFC-free BDP in patients with chronic stable asthma previously receiving CFC-BDP, from the perspective of a healthcare provider.

Symptom-free days were one of the internationally recognised outcome measures on which the economic assessments were made. Price *et al* clearly stated in the introduction to the study the rationale and support for the approach taken.

The data were analysed directly from the audited dataset of this trial. The data were not normally distributed and therefore a non-parametric statistical test was used. This was the correct method to use to analyse data of non-gaussian distribution.

As with all non-parametric statistical tests median results were presented. These were a different measure than used in Fireman *et al* study. The median values of the number of symptoms-free days were 42.4 days for patients receiving Qvar and 20 days for patients receiving CFC-BDP; p=0.006 at 12 months.

Teva stated that the objective of Fireman *et al* was to evaluate the long term (12 months) efficacy and safety of switching patients with asthma maintained on a stable dose of CFC-BDP pMDI to therapy with CFC-free BDP at approximately half their previous dose of CFC-BDP.

The efficacy measures were; patient diary card of morning and evening peak expiratory flow rate, daily asthma symptoms, sleep disturbance, number of times a ß2-agonist was used and spirometry for pulmonary function. The safety measures were; laboratory tests, including serum osteocalcin, morning plasma cortisol levels. Of the 473 patients randomised at entry into the study 354 received Qvar (CFC-free BDP) and 119 received CFC-BDP. The paper reported a statistical analysis of the individual listed symptoms of wheeze, shortness of breath or chest tightness and this was expressed as the percentage of symptom-free days (rather than individual symptom-free days). The percentage of symptom-free days experienced by patients in each treatment group were not significantly different. There was a significant difference in favour of CFC-free BDP in the percentage of days without cough and nights without sleep disturbance during months 7 to 8. The authors stated that although these differences demonstrated statistical significance they were probably not clinically significant. Symptom-free days were discussed by describing the mean percentage of symptom-free days experienced by patients in both treatment groups; 11.5% in the CFC-free BDP group and 4.6% in the CFC-BDP group. No further statistical analysis was performed, the more detailed analysis was reported by Price *et al*. Fireman concluded that the increase in 'symptom-free days' in the patients who received CFC-free BDP compared with those that received CFC-BDP was greater than a 'two fold increase'.

Teva firmly believed that Price *et al* substantiated the claim twice as many symptom-free days. Fireman *et al* and other studies did not need to be discussed as they did not have symptom-free days as a primary endpoint. Thus there was no breach of Clause 7.2.

The measurement of 'symptom-free days' in Price *et al* was a totally different measure from the prevalence of individual symptoms in patients as reported in Fireman *et al*.

Price *et al* interrogated the dataset to investigate the pharmacoeconomic aspects. Fireman *et al* interrogated the dataset to investigate safety and efficacy as measured by various primary endpoint measures detailed in the methods section of the study design. Teva therefore concluded that symptom-free days, a composite measure was a totally different measure from the prevalence of individual symptoms in patients, the two outcomes were unrelated and had no bearing on each other. It did not accept that the use of symptom-free days was either inappropriate or misleading.

Teva concluded by stating that the three studies quoted by Trinity-Chiesi to support its position had:

- Hypotheses that looked at efficacy and were powered to look at equivalence between CFC-free BDP and CFC-BDP. The studies did not have primary or secondary endpoints looking at symptom-free days.
- Had differing patient populations, namely uncontrolled asthma patients.
- Were of short duration 10-12 weeks.
- Magnussen *et al* and Davies *et al* did not record data on symptom-free days. In Gross *et al* the number of symptom-free days was recorded, this was not a primary endpoint in the study analysis or of a pharmacoeconomic investigation. The patient populations were also evaluated in different ways.

The claim was referenced to Price *et al* which was appropriate as the hypothesis of the study investigated was pharmacoeconomic and related to symptom-free days.

Despite extensive literature searches Teva had not found any other study that presented symptom-free data in patients with well controlled asthma over a 12-month period that received Qvar and CFC-BDP.

Teva therefore did not believe it was misleading to use Price *et al* as the reference and it was fair and balanced as it accurately reflected the available data on symptom-free days. Teva denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that the claim in question appeared, beneath the heading 'Doing more for your patients' on the leavepiece IV/QV/CFC/01/07. The claim was referenced to Price *et al* which was a pharmacoeconomic study based on the results of Fireman *et al*.

The Panel noted that Fireman *et al* examined whether asthmatic patients with symptoms controlled with CFC-BDP could be switched to CFC-free BDP at half the CFC-BDP dose without *inter alia*, adversely affecting the control of asthma symptoms. The authors demonstrated an overall increase in the percentage of symptom-free days (without wheeze, shortness of breath or chest tightness) between baseline and month 12 in the CFC-free BDP group (11.5%) and the CFC-BDP group (4.6%). No significant differences in the change from baseline in percentage of symptom free days were seen throughout the study. There were slight differences between CFC-free BDP and CFC-BDP in percentage of days without cough which although

statistically significant at weeks 1 to 2 and at months 7 to 8 were described as probably not clinically significant. During months 7 to 8 patients on CFC-free BDP had a significantly greater proportion of nights without sleep disturbance than patients on CFC-BDP. The study concluded that asthma control was maintained in patients switched from CFC-BDP to CFC-free BDP.

Price *et al* re-examined Fireman *et al* for the cost effectiveness study. Price defined 'symptom-free day' as the absence of all of the following: wheeze, cough, shortness of breath, and chest tightness in one day including overnight. As percentage symptom-free days were not normally distributed, median percentage symptom-free days were compared. By the end of the study patients in the CFC-free BDP group had a higher median percentage of symptom-free days than patients in the CFC-BDP group (42.4% v 20%; p=0.006). This equated to three symptom-free days per week in the CFC-free BDP group compared with 1.4 in the CFC-BDP group. The mean data which showed that the percentage of symptom-free days at 12 months was 45.6% (CFC-free BDP) and 35% (CFC-BDP), showed no statistically significant difference between the two treatment groups. This mean data appeared to be that which Fireman *et al* had used to report an increase from baseline of 11.5% (CFC-free BDP) and 4.6% (CFC-BDP) in percentage of days without wheeze, shortness of breath and chest tightness.

The Panel noted that, on a re-examination of the clinical data by Fireman *et al*, Price *et al* had reported statistically significantly more symptom-free days for patients taking CFC-free BDP compared with those taking CFC-BDP. The study authors had used a median percentage. The mean percentage did not show a statistically significant difference. The primary clinical data had not reported such a difference although there was a trend in favour of CFC-free BDP. Other studies (Davies *et al*, Gross *et al* and Magnussen *et al*) although shorter in duration (12 weeks or less) had demonstrated equivalent control of asthma for CFC-free BDP and CFC-BDP. Price *et al* was the only study to report that CFC-free BDP produced 'twice as many symptom-free days' as CFC-BDP. Overall the Panel did not consider that the data was sufficiently robust to support such a strong claim and in that regard the Panel considered that the claim 'Twice as many symptom-free days' was misleading. A breach of Clause 7.2 was ruled.

APPEAL BY TEVA

Teva submitted that this whole process became very drawn out, and one feature had been the way in which Trinity-Chiesi had written a very large number of letters in which it continually changed the basis of its complaint. Teva had provided robust answers to all of them. Additionally, some of the comments in the ruling appeared to be inconsistent or either incorrect and/or misleading.

Teva submitted that there appeared to be little acceptance or acknowledgement that the recording of individual symptoms, which included wheeze, cough, shortness of breath and chest tightness, were not interchangeable with the recording of symptom-free days and that they measured different outcomes.

Teva submitted that the studies listed by Trinity-Chiesi were not comparable and did not provide any relevant data relating to the incidence of symptom-free days in the different treatment groups. In addition, the ruling in its current form would have major implications on the way research-based companies could interpret data. This would put such companies at a disadvantage to companies that conducted minimal research and then tried to invalidate extensive studies of competitor companies and which, as in this case, demonstrated benefit to patients in a pragmatic real-life setting.

The claim 'Twice as many symptom-free days' had been used on large numbers of materials in the promotion of Qvar since 2004 and no health professional or company other than Trinity-Chiesi had complained about it.

Inconsistencies in the Panel's ruling

Gross was 'double-blind' in design

Teva submitted that the Panel's ruling provided a detailed analysis of several studies that Trinity-Chiesi claimed to demonstrate different outcomes but they were incorrectly categorised in the initial complaint. Despite several letters from Teva, Trinity-Chiesi had continued to misrepresent the studies.

The complainant alleged that 'Teva had highlighted data from a 12 month randomised, open-label trial (Firemen *et al*) and largely ignored the results from three key randomised, double-blind, double-dummy studies' (ie Gross 1999, Davies 1998 and Magnussen 2000). This statement was false as Gross *et al* was not a double-blind, double-dummy study. Gross *et al* clearly 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'. The authors seemed to claim that the study was blinded in some way but provided no details as to how this was achieved. In the 1990s there was a vogue to call a study 'single-blinded' if the patient was not told which 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 used to deliver CFC-free-BDP and CFC-BDP had different attributes as the products were present in solution and suspension respectively and had different shapes of canisters. Therefore, Teva submitted that in the absence of any details extreme caution must be exercised in relation to the claim that Gross *et al* was a blinded study as by today's standards it would be probably classed as an open-label study, as was Fireman *et al*/Price *et al*.

Teva submitted that the complaint was incorrect and misleading which unfortunately seemed to be a relatively common occurrence in the letters from

Trinity-Chiesi. Teva questioned why any company would misrepresent studies in this way but it appeared that by doing so it was seeking to strengthen its complaint in an inappropriate manner. Teva regarded this as unacceptable practice.

Parametric statistical methods

Teva submitted that the Panel's ruling stated in reference to Price *et al* that 'The mean data which showed that a percentage of symptom-free days at 12 months was 45.6% (CFC-Free BDP) and 35% (CFC-BDP), showed no statistically significant treatment differences between the two treatment groups'. This statement was untrue and was derived from an invalid use of statistical methodology.

- There was no statistical analysis conducted to determine whether the difference in mean values was statistically significant and this was clearly stated by Fireman *et al* and Price *et al*. Fireman *et al* stated that differences between treatment groups were examined statistically only for individual symptoms recorded on the case record forms. The results for symptom-free days were presented without any analysis and without comment on whether they were significant or not.

- The symptom-free days data was clearly stated by Price *et al* to have a non-Gaussian distribution and therefore it was inappropriate to consider the mean and standard deviation as an appropriate measure of the data distributions in the two treatment groups. This was clearly stated in Price *et al* and because mean and median were so far apart, non-parametric tests were required.

- If a t-test would have been performed on the data, it would have been highly significant as a t-test was more powerful than the Mann Whitney U-Test. However it would have been inappropriate to do so as the data distribution was not appropriate for use of the specific test.

- Neither Price *et al* nor Fireman *et al* conducted any statistical analysis on symptom-free days using the mean values and this was clearly indicated in the text and tables of both manuscripts.

Teva submitted that this error could be traced back to the way in which Trinity-Chiesi had conducted these complaints and it was inconceivable that a pharmaceutical company would be unaware of these basic facts. As previously pointed out to Trinity-Chiesi on several occasions Teva assumed that it was attempting to mislead the Panel.

'The mean percentage did not show a statistically significant difference'

Teva submitted that this statement in the last paragraph of the Panel's ruling was also untrue as no statistical analysis was performed in the way described in the ruling.

Review of statistical methodologies required for the analysis and interpretation of data that did not have normal (Gaussian) distribution

Teva submitted that even before a clinical trial was started power size was calculated using earlier studies which provided evidence of the variance of the data that would be studied. When a clinical trial was completed, the results were analysed using well defined statistical methodologies, supported by detailed quality assurance and internal audit. This process was required by all regulatory authorities and ensured that the results were robust and could be used to support the product that was the subject of the study. In this process one of the most important decisions that had to be taken was the choice of clinical statistical methodologies that were employed in the analysis.

Statistical test selection and data distribution

Teva submitted that to select an appropriate statistical test it was imperative to be aware of the distribution of the values presented in the data-sets because tests made assumptions about the distribution of the data and inappropriate tests could lead to incorrect statistical evaluation. One of the most commonly used tests was the (Student's) t-test as it could be easily performed and could be used when data were paired or unpaired. This test however required that the data was normally distributed which was the term used to describe a 'Gaussian distribution'. This meant that the data was symmetrically presented and the frequency of values above and below the arithmetic mean was equally distributed. If data was not 'normally distributed' it had a non-Gaussian distribution and a non-parametric test such as the Mann-Whitney U-test must be used to test the significance of difference between two treatment outcomes.

Statistical analyses significance estimation

Teva submitted that statistical analyses in clinical trials were primarily used to compare the results obtained with the different study treatments and to determine whether they were of significant proportions to reach the pre-defined level of significance. In biological/medical fields the accepted certainty was at least 95%, which was described by a 'p' value of $p \leq 0.05$ but this estimation was only valid if an appropriate test had been used.

Statistical analyses of symptom-free days in Price et al

Teva submitted that the data on symptom-free days in this study were not 'normally distributed' as stated by the author. Therefore using the arithmetic mean and the standard deviation was invalid and should not be used to describe the differences between the two treatment groups and doing so would produce a misleading conclusion. Price *et al* recognised this fact and used a Mann-Whitney U-test which was a non-parametric analysis method that was more appropriate for this type of data distribution and would provide a valid result.

Review of assessment of asthma symptoms and symptom-free days

Symptom-free days

Teva submitted that symptom-free days had been developed over the last 10 years as an important patient reported outcome measure. This measure had been developed as there was a growing awareness that asthma was a wholly treatable disease with the advent of effective inhaled corticosteroids and the newer combination therapies of inhaled corticosteroids with long-acting beta-agonists. With these treatments both patients and physicians sought to reduce the burden of asthma on the lives of sufferers. This was reflected in the British Thoracic Society's Guidance on asthma. 'The aims of pharmacological management of asthma were the control of symptoms, including nocturnal symptoms and exercise-induced asthma, prevention of exacerbations and the achievement of the best possible pulmonary function, with minimal side effects'. In addition it was now well accepted that where cost effectiveness and health economic outcomes were to be assessed symptom-free days was an appropriate measure of the impact of the disease on the ability of patients to function and hence their ability to look after themselves and to work.

Patient reported outcomes were also well accepted by the regulatory authorities and both the Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA) had produced guidance for companies and investigators who wished to conduct studies with these outcomes.

Teva submitted that patient reported outcomes were also accepted in the scientific community and the International Society for Pharmacoeconomics and Outcomes Research was formed 10 years ago and hosted several meetings each year to discuss and evaluate improvements in methodology. In this year's European Conference in Dublin (October 2007) a session was dedicated to present and discuss the perspective of the European Medicines Evaluation Agency and this session focussed on three major points that were included in the EMEA guidance.

Firstly, studies should be a minimum of 3-6 months' duration and longer if possible. This did not include run-in periods as the shorter studies were often confounded as patients would perceive an efficacy effect with a change in therapy, which could alter the patients' perception of the level of their disability due to the occurrence of symptoms.

Secondly, it was stated that asthma was one of the most appropriate diseases in which to use patient reported outcomes as an outcome measure as it was a chronic disease with a relatively low mortality rate. However care should be taken to ensure that the study was conducted over long-enough periods to ensure that seasonal differences and episodic exacerbations did not bias the results.

Thirdly, it was reinforced that if patient reported outcomes were to be used as an endpoint, then it was important to select an appropriate sample size that was supported by earlier studies that might include Phase II work.

Teva submitted that there was considerable support for the view that if a patient reported outcome was to be measured such as quality of life and symptom-free days the study should be longer than 6 months and preferably one year in duration.

Symptom-free days had now been used for many years as a measure of asthma therapy effectiveness and for the analysis of cost effectiveness (Malone *et al* 2003, Price *et al*) and Teva had provided a list of 199 studies which referred to symptom-free days 127 of which included this as an outcome measure. The studies included the commonly used medicines including Seretide, Symbicort, budesonisde, ciclesonide and many other medicines. Symptom-free days were therefore a commonly used and well accepted end point for analyses in clinical studies.

Asthma symptoms vs. symptom-free days

Teva submitted that the assessment of symptom-free days must not be confused with traditional assessment of listed symptoms. Historically, asthma studies had recorded the occurrence and severity of symptoms that were related to asthma, and analysed them in the traditional way. Often there were few differences as the studies were inadequately powered for this measure and their relevance was often questioned. If a patient was treated for asthma the most important question to them was whether they felt well and could function in the normal way. A measure of this was now accepted to be measured by health related quality of life questionnaires and assessments of symptom-free days.

Teva submitted that Price *et al* defined a symptom-free day as 'an absence of wheeze, cough, shortness of breath and chest tightness in one day, including overnight'. This was very different from the occurrence of asthma symptoms and this was easily illustrated. A patient might report that they suffered from 6 symptoms in a week and these might include 3 attacks of wheeze that required use of their reliever medication (short acting beta agonists), one episode of tightness of the chest, one episode of shortness of breath and one episode of cough. This could give the impression that this patient was very unwell and it could indicate that on 6 days a patient could have experienced a symptom that impaired their ability to function. Equally, it could also be the case that a patient suffered from 6 symptoms that were caused by three attacks of wheeze on one day and that the patient remained well for the remaining six days during the week. This would be considered to be an acceptable result by both physician and patient.

Teva submitted that in Fireman *et al* and Price *et al* the symptom-free days results were clearly defined and were used as a measure of effectiveness of the two test products in accordance with usual practice and formed the basis of the cost-effectiveness analysis. This was appropriate, conformed to current guidelines and showed a clear benefit for Qvar compared with CFC-BDP.

Teva submitted that symptom-free days and asthma symptoms measured and assessed different established outcomes. The results were neither comparable nor interchangeable, but both were defined and accepted by the major regulatory authorities in Europe and North America.

Review of the clinical studies contained in the Panel ruling

Teva noted that in the Panel ruling four clinical studies were evaluated (Gross *et al*, Davies *et al*, Magnussen *et al*, Fireman *et al* and Price *et al*) but key differences between them had been ignored by Trinity-Chiesi despite this being the subject of several letters to the company. 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). Teva submitted that studies could only be compared if they were comparable in these evaluations and in this case it was clear that this was not so.

Study selection

Teva submitted that of the four studies in the discussion only Gross *et al* and Fireman *et al* and Price *et al* presented statements relating to use of symptom-free days. Davies *et al* and Magnussen *et al* did not measure symptom-free days. Therefore as this complaint was based on the interpretation of symptom-free days and as this measure was totally different from an analysis of individual symptoms, these studies should be disregarded from the ruling and were irrelevant to this appeal.

Teva submitted that of the studies described above only Fireman *et al* and Price *et al* provided any data concerning symptom-free days. Gross *et al* claimed that there were no differences between the groups but presented no data to support this statement and in the absence of any data indicating the values and 95% confidence intervals this statement must be interpreted with extreme caution. Conversely Fireman *et al* and Price *et al* presented full data on the median values of the symptom-free days and the 95% confidence intervals and as the study was conducted over 12 months the conclusions were robust. Teva submitted that in a recent discussion with Professor Price he had fully supported this conclusion. Fireman *et al* and Price *et al* presented full data and there were twice as many symptom-free days in Qvar patients compared with those receiving CFC-BDP as defined by appropriate non-parametric statistical methodology.

Objectives

Teva noted that the objective of Gross *et al* was to confirm if '[due to] improved lung deposition of [CFC-free BDP] in comparison to CFC-BDP … lower doses of [CFC-free BDP] may be required to provide adequate asthma control'. The primary endpoint variable was 'morning peak expiratory flow over weeks 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.

Teva noted that 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 [pressurised metered dose inhaler] to therapy with [Qvar] 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 peak expiratory flow (am and pm), forced expiratory volume over 1 second, daily asthma symptoms and number of times beta agonists were used, were recorded.

Teva noted that the objective of Price *et al* was 'To compare the cost effectiveness of … 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 and drug-only direct healthcare costs'.

Sample size

Teva noted that in Gross *et al*, a total of 113, 117 and 117 patients were enrolled into the three treatment groups of CFC- free BDP, CFC-BFD and CFC-free placebo respectively.

Teva noted that Fireman *et al* and Price *et al* had a total 473 of which 350 patients received CFC- free BDP and 118 (intention-to-treat (ITT) analysis) patients received CFC-BDP. Therefore, as Fireman *et al* contained a much larger sample size, it had a significantly greater statistical power than Gross *et al* so it was not surprising that Fireman *et al* could detect differences which Gross *et al* could not.

Teva submitted when evaluating a study it was usual practice to enrol enough patients in to a study to ensure that any conclusion was robust and could withstand scrutiny. In the 1980s and 1990s 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 it became common practice to determine sample size that was required based on previous pilot studies, which although were too small to provide a reliable conclusion provided an assessment of the likely difference in outcomes that would be encountered in conducting 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.

Study design and study medication

Teva submitted that 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.

Run-in period

Teva submitted that oral steroids modified the symptoms in asthma and this difference alone could make these studies incomparable. Gross *et al* treated all patients with 30mg oral prednisolone for 7-12 days and demonstrated reversibility of asthma symptoms as assessed by at least 15% increase of am PEFR. In a striking contrast, patients in Fireman *et al* and Price *et al* were not allowed to have any steroids for 30 days before entry into the study. This was a major difference between the two studies and symptom assessments after 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. Conversely, Fireman *et al* and Price *et al* 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.

Teva therefore submitted that these studies were not comparable and it was inappropriate to make the value judgements listed in the Trinity-Chiesi complaint and the Panel ruling.

Study Duration

Teva noted that Fireman et al, Price *et al* and Gross *et al* had very different study durations.

- Gross *et al* was conducted with a 10-12 day run-in period followed by 12 weeks' treatment with study medicine.
- Fireman *et al* and Price *et al* were conducted for a 12 month period with no oral steroid run-in period.

Study Medication

Teva noted that in Gross *et al* patients were randomised to receive either CFC- free BDP at 400mcg/day or CFC-BDP 800mcg/day following the 7-12 day oral steroid therapy. This medication schedule was biased in favour of the CFC-BDP and as the patients had uncontrolled asthma as defined by the fact that they had experienced symptoms in the last 5 days of the run-in period, the dose of CFC- free BDP was lower than that licensed for use in the UK. The Qvar SPC stated that a 2:1 dose ratio of Qvar to CFC-BDP was licensed for use in controlled patients and patients with uncontrolled asthma should change to Qvar at a 1:1 dose compared with CFC-BDP. This was a major confounding factor in this study design and medication selection. Conversely, Fireman *et al* and Price *et al* only admitted patients whose asthma was controlled 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

Teva submitted that the most fundamental difference between these studies was that the patients in each differed significantly in degree of the control of their symptoms before enrolment. These differences alone might already account for any changes seen later in the study.

Teva submitted that 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]' (emphasis added). Gross *et al* defined asthma symptoms as a mean morning peak expiratory flow between 50% and 80% of predicted normal value plus one of the following: sleep disturbance on ≥1 nights; presence of 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 months' history of asthma (and stable symptoms for the past month) were enrolled' (emphasis added).

Teva submitted that the patient populations were therefore not comparable in many ways. This was an important difference and now there was 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.

Detailed analysis and discussion relating to each of the points raised in the ruling and how these relate to the clinical manuscripts and conclusions

Teva submitted that Fireman *et al* and Price *et al* were much more representative of the patient types seen in general practice and the different patient types used compared to Gross et al made it impossible to obtain useful data by comparing the studies. Fireman *et al* conducted the study over a 12 month period and provided data analysed correctly by non-parametric statistical methods and presented it in a robust and correct manner. The results showed that patients treated with CFC- free BDP experienced 42.4% of symptom-free days (median; 95% CI of 32.1-57.9) whilst those treated with CFC-BDP experienced only a 20.0% (median; 95% CI of 3.8-37.9). These differences were highly significant with a p value of p=0.006. Therefore patients receiving Qvar experienced twice as many symptom-free days than those receiving CFC-BDP and this difference was highly significant.

Teva submitted other studies included by Trinity-Chiesi in its complaint provided no data concerning symptom-free days and in two of the studies symptom-free days were not measured. Individual asthma symptoms were a different outcome from symptom-free days and could not be interchanged. These studies of Gross *et al*, Magnussen *et al* and Davies *et al* could not therefore provide any useful data or contribute to the discussion of symptom free days and therefore the complaint was without merit.

Teva submitted that even if the symptom-free days had been measured the studies used short-term designs that did not comply with current guidelines for duration of studies reporting patient reported outcomes, enrolled different patient populations and 2/3 of the studies used large doses of oral steroids in the initial run-in phase. Additionally the numbers of patient in these studies were also too small to reliably detect any change in symptom-free days so it was not surprising that Gross *et al*, which claimed to assess them, failed to find a difference. These studies were claimed to be 'key studies' by Trinity-Chiesi which clearly they were not and were simply misrepresented in the complaint.

Therefore Teva submitted that the claim 'Twice as many symptom-free days' was clear and factually accurate and the study that presented data on this endpoint was well designed, conducted at the correct dose for controlled patients, with an appropriate duration that was in compliance with current guidelines and presented a valid statistical analysis.

Teva submitted that the data was thus correct, was fair and balanced and there were no relevant studies that contradicted this finding in relation to the endpoint of symptom-free days.

Review of possible mechanisms of how Qvar provided greater efficacy than CFC-BDP which resulted in twice as many symptom-free days and the possible interpretation by the prescriber.

Teva submitted that this was in keeping with known attributes of Qvar which had a small particle size which resulted in greater lung deposition than CFC-BDP. The presence of extra-fine particles resulting in increased lung deposition provided Qvar with increased efficacy which was why it was used at a lower dose than CFC-BDP in controlled patients with an efficacy ratio of 2:1 (Qvar to CFC-BDP). Therefore a physician would take from these data that Qvar was more potent than CFC-BDP and therefore it was not surprising that Qvar was associated with an improved outcome of patients with an increase in symptom-free days. In addition these findings were entirely consistent with the quality of life assessments published for the same study by Juniper *et al* (2002) which also demonstrated benefit for patients receiving Qvar.

The fact that patients received benefit from Qvar over and above that seen by CFC-BDP was therefore correct.

Teva did not agree with the conclusion that the claim 'Twice as many symptom-free days contravened Clause 7.2.

COMMENTS FROM TRINITY-CHIESI

Trinity-Chiesi stated that the vast majority of Teva's appeal went into details that were not relevant to the central issue which was did the claim of 'Twice as many symptom-free days' in its current form breach Clause 7.2, ie 'Information, claims and comparisons must be accurate, balanced, fair, objective, unambiguous and must be based on an up to date evaluation of all the evidence and reflect that evidence clearly …'? Trinity-Chiesi alleged that this claim was in breach of Clause 7.2.

Trinity-Chiesi noted Teva had stated that the whole process had become very drawn out and one feature had been the way in which Trinity-Chiesi had written a very large number of letters in which it continually changed the basis of its complaint, and Teva had provided robust answers to all of them. Additionally, Teva had noted that some of the comments in the ruling appeared to be inconsistent and could be considered either incorrect or misleading. Trinity-Chiesi stated that its responses to Teva and the Panel were within the required timeframe of ten working days. The volume of correspondence sent to Teva reflected the changing Qvar promotional campaigns from the 'Think small – make a big difference – opportunity to do more' campaign with a Bonsai tree to the 'Doing more for patients' campaign with the beach holiday scene. The letter from the Panel detailing its ruling was dated 19 October and Teva's subsequent appeal was dated 16 November 2007 which was significantly beyond the ten working days from when an appeal must be lodged. Furthermore, since the Panel ruling, journal advertisements stating this claim had continued to appear regularly in various journals including Pulse and The Pharmaceutical Journal.

Trinity-Chiesi noted that Teva was particularly concerned that there appeared to be little acceptance or acknowledgement that the recording of individual symptoms, which included wheeze, cough, shortness of breach and chest tightness, were not interchangeable with the recording of symptom-free days and that they measured different outcomes. Trinity-Chiesi did not suggest that the parameter of symptom-free days was interchangeable with asthma symptoms however, the data on asthma symptoms in Fireman *et al* should be discussed alongside the 'symptom-free days' data as it was very relevant to the recipient of Qvar promotion and provided prescribers with a greater understanding of the outcomes related to asthma symptoms in this study when considering using Qvar. Without this information the claim was unbalanced and potentially misleading.

With regard to Teva's view that the studies listed in the complaint were not comparable and did not provide any relevant data relating to the incidence of symptom-free days in the different treatment groups, Trinity-Chiesi stated it was not for Teva to decide whether a study that has assessed symptom-free days was relevant to health professionals. Teva was obliged to reflect and/or discuss all the evidence in a fair and balanced manner and allow health professionals to draw their own conclusions on whether Gross *et al* was relevant to their practice. As stated above, data on asthma symptoms was of relevance to prescribers when discussing symptom-free days particularly as the same four asthma symptoms were assessed in all three of these studies (Gross *et al*, Davies *et al* and Magnussen *et al*) as well as in Fireman *et al*.

In response to Teva's view that the Panel's ruling

would have major implications on the way research-based companies could interpret data which would put such companies at a disadvantage to companies that conducted minimal research and then tried to invalidate extensive studies of competitor companies and which, as in this case, demonstrated benefit to patients in a pragmatic real-life setting, Trinity-Chiesi stated that 3M as a research-based company clearly conducted a number of trials on Qvar before selling on the marketing and distribution rights. Chiesi was also a research-based company and would equally be concerned should the above suggestion be substantive, however, this was a deliberate distraction from the central issue which was, did the claim 'Twice as many symptom-free days' in its current form breach Clause 7.2? As stated above, Teva had an obligation to reflect and/or discuss all the evidence in a fair and balanced manner and allow the health professionals to draw their own conclusions on whether the data reflected a pragmatic life setting in contrast to other studies that had assessed symptom-free days and asthma symptoms in a controlled environment.

In response to Teva's submission that the claim 'Twice as many symptom-free days' had been used since 2004 without complaint from a health professional or another company, Trinity-Chiesi stated that the fact that Teva had not received any complaints previously was irrelevant and did not support the notion that the claim was therefore acceptable. It should be noted that during that time no other company was actively promoting a CFC-BDP or CFC-free BDP metered dose inhalers and Teva's claims were most probably much less scrutinised.

In response to Teva's submission that the Panel had provided a detailed analysis of several studies that claimed to demonstrate different outcomes but these were incorrectly categorised in the initial complaint and that despite several letters Trinity-Chiesi had continued to misrepresent these studies, Trinity-Chiesi noted that Teva had specifically clarified this minor oversight (Gross *et al* – described as a blinded study whereas Davies *et al* and Magnussen *et al* were described as double-blind, double dummy studies) in its response to the complaint. It was Trinity-Chiesi's understanding that the Panel was aware of this oversight before it considered the matter and ruled the claim in breach of Clause 7.2.

Trinity-Chiesi stated that Teva's discussion around the statistics was a deliberate distraction and peripheral to the central issue which was, did the claim 'Twice as many symptom-free days' in its current form represent all the relevant available evidence?

Trinity-Chiesi noted that in Teva's response to the complaint it described Price *et al* (published in Pharmcoeconomics) as a refereed, vetted, prestigious, widely read journal and suggested that consequently the published information should be accepted as being correct. Similarly, Gross *et al* was published in Chest, which Trinity-Chiesi considered to be an equally highly respected respiratory journal. However, Teva's appeal had speculatively challenged the foundations of this study substantially which contrasted with Teva's previous viewpoint on Price *et al*.

The lung function parameters measured in Gross *et al*, Davies *et al*, Magnussen *et al* and Fireman *et al* could not support the claim that Qvar provided greater efficacy than CFC-BDP at comparable licensed doses.

Trinity-Chiesi reaffirmed its position that the claim 'Twice as many symptom-free days' was in breach of Clause 7.2.

APPEAL BOARD RULING

The Appeal Board noted that the claim 'Twice as many symptom-free days' was referenced to Price *et al* which was a pharmacoeconomic study based on the clinical results of Fireman *et al*.

Fireman *et al* evaluated whether asthma patients with symptoms controlled with CFC-BDP could be switched to CFC-free BDP at half the CFC-BDP dose without, *inter alia*, adversely affecting the control of asthma symptoms. Throughout the one year study patients recorded their daily asthma symptoms (wheeze, cough, shortness of breath and chest tightness) on a scale of 0 to 5 and the number of times they used a reliever inhaler. The authors recorded that there were no consistent differences between the treatment groups with regard to individual asthma symptoms or daily use of reliever inhalers. Both groups recorded an increase in percentage of symptom-free days between baseline and one year (CFC-BDP 4.6% vs CFC-free BDP 11.5%). The authors concluded that asthma control was maintained in both groups.

Based on the clinical data generated by Fireman *et al*, Price *et al* compared the cost effectiveness of CFC-free BDP with CFC-BDP. Price *et al* assessed asthma symptoms in terms of symptom-free days which was a composite end point defined as the absence of all of the following: wheeze, cough, shortness of breath and chest tightness, in one day (including overnight). A table of data recorded the percentage symptom-free days and showed at baseline the median percentage symptom-free days in the CFC-free BDP group was 21.4% [95% confidence interval 14.3-28.6] and in the CFC-BDP group it was 12.7% [6.7-28.6] (p=0.226), ie there was almost a two fold difference between the groups at baseline. This difference was maintained throughout the study such that after one year the median percentage symptom-free days in the CFC-free BDP group was 42.4% [32.1 – 57.9] and 20% [3.8 – 37.9] in the CFC-BDP group. The Appeal Board noted that the confidence intervals overlapped. It was this data which formed the basis of the claim 'Twice as many symptom free days'.

The Appeal Board did not consider that Price *et al* was sufficiently robust as to support the claim 'Twice as many symptom free days'. The data had been derived from a pharmacoeconomic evaluation of primary clinical data in which no difference between CFC-free BDP and CFC-BDP in terms of asthma control had been shown. There was no indication in Price *et al* to show that the study had been powered to detect a statistical difference in percentage symptom-free days;

there had, in any case, been a two-fold difference between the two treatment groups at baseline in this regard, a difference which was present at the end of the study. The Appeal Board considered that given the data on which it was based the claim at issue was misleading and upheld the Panel's ruling of a breach of Clause 7.2. The appeal was unsuccessful.

Complaint received	**31 May 2007**
Case completed	**9 January 2008**