CASE AUTH/1833/5/06

ASTRAZENECA v GLAXOSMITHKLINE

CONCEPT study leavepiece

AstraZeneca complained that a leavepiece issued by Allen & Hanburys, part of GlaxoSmithKline, did not present a fair and balanced account of the CONCEPT (CONtrol CEntred Patient Treatment) study which had compared stable dosing of GlaxoSmithKline's product Seretide (salmeterol/fluticasone propionate) with symptom led (variable) dosing of AstraZeneca's product Symbicort (formoterol/budesonide) in the management of asthma. The leavepiece implied that Seretide was compared with clinically equivalent doses of Symbicort as it did not explicitly state that like-for-like steroid doses were not used (82% Symbicort patients were stepped down to the lowest possible dose, compared with all Seretide patients being maintained at 500mcg per day). The leavepiece did not explicitly state that in the Symbicort arm the steroid dose could only be increased in response to symptoms, thus predetermining a higher symptom level in this group. The leavepiece did not reflect the balance of the evidence in that it did not refer to the results of the SUND study (where comparable steroid doses were used, which resulted in significantly fewer exacerbations in the Symbicort arm).

The CONCEPT study had consisted of a 2 week run-in, a 4 week stabilisation phase and a 48 week variable maintenance phase. During the 4 week stabilisation phase patients remained on either Seretide 250mcg bd or Symbicort 200mcg 2 puffs bd which equated to comparing a daily dose of 500mcg fluticasone with 800mcg budesonide (delivered via a turbohaler device) respectively. AstraZeneca stated that these doses were approximately equivalent.

Following 4 weeks on approximately equivalent doses patients entered the variable maintenance phase if they were completely symptom free. During the variable maintenance phase, Seretide patients remained on fixed Seretide 250mcg 1 inhalation bd. Symbicort patients could adjust their therapy according to a predefined treatment plan; they could halve their dose and subsequently step up or down as indicated by the presence or absence of various asthma symptoms and changes in morning peak expiratory flow measurements. If Symbicort patients were well controlled they were instructed to further reduce the dose to only 1 inhalation once daily in the evening which equated to a daily steroid dose of only 200mcg of budesonide. This was important as Seretide patients remained on a fixed daily dose of 500mcg fluticasone.

Results showed that during the variable maintenance phase 82% of Symbicort patients stepped down to 1 inhalation per day at some time during the trial. Only when they developed symptoms were they instructed to step up the dose to regain asthma control. Thus the majority of Symbicort patients were instructed to down titrate to the lowest possible maintenance dose of inhaled steroid and remain on this dose until they developed asthma symptoms. It was therefore not surprising that these patients experienced more asthma symptoms and exacerbations compared to those taking comparatively higher steroid levels of Seretide 250mcg bd.

The dose for dose steroid comparison chosen for this trial was alleged to be unfair and likely to have significantly influenced the efficacy results. In order to fairly compare two different treatment approaches for asthma using either a fixed or an adjustable dosing regime one would need to have compared a more equivalent overall dose for dose steroid comparison.

Furthermore, the summaries of product characteristics (SPCs) for Symbicort and Seretide supported a reduction in dosing to 1 puff daily. The CONCEPT study design did not allow well controlled Seretide patients to step down to once daily dosing as recommended in the SPC. Restricting once daily dosing to Symbicort created an unfair dose comparison increasing the probability of a favourable outcome for patients taking twice daily Seretide.

AstraZeneca stated that it had conducted 8 studies, involving over 10,000 patients, using Symbicort as an adjustable dosing regime whereby patients could adjust therapy according to a patient asthma management plan. In all of these trials patients could down titrate their Symbicort dose if well controlled to a minimum dosage of 2 inhalations per day. In those trials comparing adjustable maintenance dosing with fixed dosed Symbicort, adjustable maintenance dosing provided at least as good or superior asthma control compared to fixed

dose Symbicort but at reduced overall medication doses. AstraZeneca noted in particular that the SUND study demonstrated that Symbicort adjustable maintenance dosing was equivalent in terms of achieving the primary endpoint of odds of achieving a well-controlled asthma week compared to fixed dose Seretide and significantly more effective at reducing the clinically important secondary endpoint of severe exacerbations.

AstraZeneca submitted that the previous studies, in contrast to the CONCEPT study, had shown adjustable dosing with Symbicort to be either as or more efficacious than using fixed dose maintenance therapy. This was because the dosing regimes used in the previous studies had been more equivalent.

Finally, recent research indicated that in normal clinical practice only 0.3% of patients were instructed by their health professional to take Symbicort at all strengths 1 puff once daily. Hence the doses of Symbicort used in the CONCEPT study did not reflect UK clinical practice.

AstraZeneca noted that the CONCEPT study design depicted in the leavepiece did not show that the majority of Symbicort patients were down-titrated to one inhalation a day. This was important as the relative doses of corticosteroid used in the maintenance part of the study were a critical determinant in the evaluation of relative efficacy. Hence the statement regarding once daily dosing in small font at the bottom was not sufficiently prominent nor did the page indicate the high percentage of Symbicort patients (82%) who were down-titrated to 1 inhalation daily at some point in the trial. Not including this data was clearly misleading and unfair and did not allow the reader to reach a balanced view.

AstraZeneca alleged that the claim 'Seretide stable dosing achieves superior asthma control compared to formoterol/budesonide symptom led dosing' was all encompassing, exaggerated and misleading and did not reflect fairly the body of clinical evidence. Also the symptom led dosing approach used in the study was not one that was used routinely in clinical practice.

The Panel noted that CONCEPT was a comparative study of two different treatment approaches for asthma – fixed maintenance dosing with Seretide or adjustable maintenance dosing with Symbicort. Patients in the study were previously symptomatic on either 200-500mcg inhaled corticosteroid plus long acting beta$_2$ agonist or >500-1000mcg inhaled corticosteroid alone. Patients were initially stabilized, over four weeks, on Seretide 250 1 puff twice daily (total daily dose (tdd) salmeterol 100mcg/fluticasone 500mcg) or Symbicort 2 puffs twice daily (tdd formoterol 24mcg/budesonide 800mcg twice daily). During this stabilization phase, when both groups received fixed doses, the percentage of symptom-free days was similar between the two treatments. Having been stabilized over 4 weeks, patients in the Symbicort group were instructed to halve their dose to 1 puff twice daily (tdd formoterol 12mcg/budesonide 400mcg). At subsequent clinic visits patients who continued to be controlled could halve the dose again to 1 puff daily (formoterol 6mcg/budesonide 200mcg daily). Such low dosing was not inconsistent with the Symbicort SPC. If after stepping down to this lowest dose patients subsequently lost control of their asthma, as defined by certain criteria, they were instructed to go back to not less than 1 puff twice daily (tdd formoterol 12mcg/budesonide 400mcg) throughout the rest of the 52 week period. The study was not a comparison of steroid dose *per se*.

During the course of the study 83.1% of patients in the Symbicort group stepped down their dose to 1 puff daily at some time and 41.6% increased their dose to 4 puffs twice daily for 7-14 days at least once. Over the 52 week treatment period the mean daily dose of fluticasone (from Seretide two puffs daily) was 463mcg and the mean daily dose of budesonide (from adjustable dosing of Symbicort) was 480mcg. Diary card data showed that Symbicort patients used a mean of 1.8 inhalations daily (equivalent to 360mcg budesonide).

The Panel noted that the leavepiece did not detail the mean daily dose of product or the mean daily number of inhalations. Further the leavepiece gave no details as to how patients, in practice, had adjusted the dose of Symbicort. It was thus difficult for readers to fully understand the clinical significance of the results. The Panel considered that in this regard the leavepiece was misleading. Breaches of the Code were ruled.

The Panel noted AstraZeneca's comments regarding the design of the CONCEPT study, the fact that its results seemed to contradict other studies and that the symptom led dosing approach used was not one that was routinely used in clinical practice. However, other studies had been open-label as opposed to the CONCEPT study which was double-blind. Additionally the CONCEPT study had allowed Symbicort to be dosed at 1 puff daily which, although lower than in other studies, was nonetheless consistent with the Symbicort SPC. In that regard, whilst noting its ruling above, the Panel did not consider that claims such as 'Seretide stable dosing achieves superior asthma control compared to formoterol/budesonide symptom led dosing' regarding the symptom led dosing of Symbicort *per se* were misleading. No breaches of the Code were ruled.

AstraZeneca UK Limited complained about a leavepiece (ref SFL/LVP/05/19527/2-FP/July 2005) issued by Allen & Hanburys Limited, part of GlaxoSmithKline UK Ltd. The leavepiece concerned the CONCEPT (**CON**trol **CE**ntred **P**atient **T**reatment) study which compared stable dosing of GlaxoSmithKline's product Seretide (salmeterol/fluticasone propionate) with symptom led (variable) dosing of AstraZeneca's product Symbicort (formoterol/budesonide).

COMPLAINT

AstraZeneca alleged that the leavepiece did not present a fair and balanced representation of the data in breach of Clauses 7.2 and 7.3 of the Code.

The leavepiece compared two different approaches for asthma control, however:

- it implied that Seretide was compared with clinically equivalent doses of Symbicort as it did not explicitly state that like-for-like steroid doses were not used (82% Symbicort patients were stepped down to the lowest possible dose, compared with all Seretide patients being maintained at 500mcg per day),
- it did not explicitly state that in the Symbicort arm the steroid dose could only be increased in response to symptoms, thus predetermining a higher symptom level in this group,
- it did not reflect the balance of the evidence in that it did not refer to the results of the SUND study (where comparable steroid doses were used, which resulted in significantly fewer exacerbations in the Symbicort arm).

Study design and relative inhaled steroid doses chosen

AstraZeneca explained that the CONCEPT study design, as outlined in the leavepiece, consisted of a 2 week run-in, a 4 week stabilisation phase and a 48 week variable maintenance phase. During the 4 week stabilisation phase patients remained on either Seretide 250mcg bd or Symbicort 200mcg 2 puffs bd which equated to comparing a daily dose of 500mcg fluticasone with 800mcg budesonide (delivered via a turbohaler device) respectively. These doses of the two inhaled corticosteroids were considered to be approximately equivalent. According to its summary of product characteristics (SPC) fluticasone was twice as potent as budesonide. In section 4.2 of the fluticasone SPC under posology and method of administration '100mcg of fluticasone propionate is approximately equivalent to 200mcg dose of beclometasone dipropionate (CFC containing) or budesonide'.

Following the 4 weeks stabilisation phase on approximately equivalent doses patients then entered the variable maintenance phase if they were completely symptom free. During the variable maintenance phase, patients in the Seretide arm remained on fixed Seretide 250mcg 1 inhalation bd. Symbicort patients were able to adjust their therapy according to a predefined treatment plan; they could halve their dose and subsequently step up or down as indicated by the presence or absence of various asthma symptoms and changes in morning peak expiratory flow measurements. If patients in the Symbicort arm were well controlled, they were instructed to further reduce the daily dose to only 1 inhalation once daily in the evening. One inhalation per day of Symbicort dose equated to a total inhaled steroid daily dose of only 200mcg of budesonide when delivered via a turbohaler device. This was important as Seretide patients remained on a fixed Seretide dose that equated to a total inhaled steroid daily dose of 500mcg fluticasone.

According to the published CONCEPT paper, during the variable maintenance phase 82% of Symbicort patients stepped down to 1 inhalation per day at some time during the trial. Only when they developed symptoms were they then instructed to step up the dose again to achieve asthma control. This meant that the majority of patients taking Symbicort were instructed to down titrate to the lowest possible maintenance dose of inhaled steroid and remain on this dose until they developed asthma symptoms. It was therefore not surprising that these patients experienced more asthma symptoms and exacerbations compared to those taking comparatively higher steroid levels of Seretide 250mcg bd.

The dose for dose steroid comparison chosen for this trial was therefore unfair and likely to have significantly influenced the efficacy results for this trial. In order to fairly compare two different treatment approaches for asthma using either a fixed or an adjustable dosing regime one would need to have compared a more equivalent overall dose for dose steroid comparison.

Comparative SPC dosing recommendations

Furthermore, the SPCs for Symbicort and Seretide supported a reduction in dosing to 1 puff daily. The Symbicort SPC stated 'in usual practice when control of symptoms is achieved with the twice daily regimen, titration to the lowest effective dose could include Symbicort Turbohaler given once daily, when in the opinion of the prescriber, a long-acting bronchodilator would be required to maintain control'. Similarly the Seretide SPC stated 'Where the control of symptoms is maintained with the lowest strength of the combination given twice daily then the next step could include a test of inhaled corticosteroid alone. As an alternative, patients requiring a long acting beta-2-agonist could be titrated to Seretide given once daily if, in the opinion of the prescriber, it would be adequate to maintain disease control'.

The CONCEPT study design did not allow well controlled Seretide patients to step down to once daily dosing as recommended in the SPC. Restricting once daily dosing to Symbicort created an unfair dose comparison between the two groups hence increasing the probability of a favourable outcome for patients taking twice daily Seretide.

Contradicts the balance of evidence supporting adjustable maintenance dosing vs fixed dosing

AstraZeneca stated that it had conducted 8 studies involving over 10,000 patients using Symbicort as an adjustable dosing regime whereby patients could adjust therapy according to a patient asthma management plan. In all of these trials patients could down titrate their Symbicort dose if well controlled to a minimum dosage of 2 inhalations per day. In those trials comparing adjustable maintenance dosing with fixed dosed Symbicort, adjustable maintenance dosing provided at least as good or superior asthma control compared to fixed dose Symbicort but at reduced overall medication doses.

Another trial compared adjustable dosing Symbicort with fixed dose Seretide. The AstraZeneca SUND study compared a fairer overall dose for dose inhaled corticosteroid comparison. In the SUND study, patients could adjust their Symbicort 200mcg dose down to a minimum of 2 inhalations per day whilst patients remained on a fixed dose of Seretide 250mcg twice daily. The design of the SUND study attempted

to select a fair dose for dose comparison so that the two different treatment approaches could be fairly evaluated. Symbicort patients could adjust their dose using a defined patient management plan, from 2 to 8 inhalations per day depending on asthma control. An open design was selected for this trial due to the practicable difficulties for patients in using a double-dummy study design for such comparison.

The SUND trial demonstrated that Symbicort adjustable maintenance dosing was equivalent in terms of achieving the primary endpoint of odds of achieving a well-controlled asthma week compared to fixed dose Seretide. However it also demonstrated that adjustable Symbicort was significantly more effective at reducing the clinically important secondary endpoint of severe exacerbations by 40% compared to fixed dose twice daily Seretide. Overall patients in the Symbicort adjustable dosing group used a mean of 544mcg/day of budesonide versus 500mcg/day of fluticasone in the Seretide fixed dosing group during the entire study.

Hence these trials in a large number of patients had shown adjustable dosing with Symbicort to be either as or more efficacious than using fixed dose maintenance therapy either as Symbicort or Seretide. The difference compared to the CONCEPT trial related to the dosing regime selected. In the aforementioned trials a more equivalent inhaled steroid dose for dose comparator between adjustable and fixed dosing was selected.

An independent article (Murphy 2005) outlined the case for improving asthma care for patients by outlining the treatment options and the different treatment approaches. In the section on fixed versus adjustable therapy the author discussed the clinical data to support the respective approaches. The fifth paragraph detailed the CONCEPT study and stated: 'However the results of the study need to be interpreted carefully. This study contradicts the findings of eight other studies investigating adjustable maintenance dosing with the formoterol/budesonide combination. The mean dose of the formoterol/budesonide combination used in this study was 1.8 inhalations per day, with 82% of patients on a maintenance dose as low as one inhalation per day, while patients in the salmeterol/fluticasone arm were maintained throughout on two inhalations per day'.

Finally, recent research indicated that in normal clinical practice only 0.3% of patients were instructed by their health professional to take Symbicort at all strengths 1 puff once daily. (As assessed by AstraZeneca using IMS Disease Analyzer December 2005). Hence the doses chosen by the CONCEPT study for Symbicort did not reflect actual clinical practice in the UK.

In view of the above, AstraZeneca alleged that the CONCEPT study leavepiece was in breach of Clauses 7.2 and 7.3.

1 'A comparison of two treatment approaches for asthma'

Page 1 of the leavepiece described the objectives of the CONCEPT trial with an illustration of the study design. The study design illustrated the different stages and dosing regimes used in the two arms of the trial. However it did not illustrate that the majority of Symbicort patients were down-titrated to one inhalation a day. This was important as the relative doses of corticosteroid used in the maintenance part of the study were a critical determinant in the evaluation of relative efficacy. Hence the statement regarding once daily dosing in small font at the bottom was not sufficiently prominent nor did the page indicate the high percentage of Symbicort patients (82%) who were down-titrated to 1 inhalation daily at some point in the trial. Not including this data was clearly misleading and unfair and did not allow the reader to reach a balanced view and was therefore in breach of Clauses 7.2 and 7.3.

2 'Seretide stable dosing achieves superior asthma control compared to formoterol/ budesonide symptom led dosing'

Pages 2 and 3 of the leavepiece outlined the results from the CONCEPT trial. The nature of the CONCEPT study design, as discussed, meant that these statements were all encompassing, exaggerated and misleading and did not reflect fairly the body of clinical evidence.

Also the symptom led dosing approach used in the study was not one that was used routinely in clinical practice and hence these statements were in breach of Clauses 7.2 and 7.3.

In conclusion, AstraZeneca considered that this promotional use of the CONCEPT study represented a serious breach of the letter and the spirit of the Code and due to the nature of these breaches sought immediate withdrawal of this item and any other promotional items that detailed the CONCEPT results in this manner.

RESPONSE

GlaxoSmithKline stated that the promotion of the CONCEPT study had been the subject of intercompany dialogue without resolution although it had agreed to include comments on the average steroid dose in each arm of the study as part of a conciliatory process to resolve the differences without recourse to the Authority.

As regards the leavepiece itself, GlaxoSmithKline did not agree that it was in breach of the Code for the following reasons:

- It represented an important and clinically relevant study that compared two different approaches for asthma control that were within the SPC recommendations for both products. It compared alternative dosing regimes that could be used for asthmatic patients, but did not imply that Seretide was compared with pharmacologically equivalent doses of Symbicort. GlaxoSmithKline noted that the study addressed a question that was particularly relevant to clinical practice and in that regard was a valid and fair comparison of therapeutic options. The depiction of the study design and the accompanying bullet points stated quite clearly that the objective of the CONCEPT

study was to compare the effect of two different treatment approaches on asthma control, a stable dosing approach and a symptom led dosing approach. This comparison was represented in the diagram with symptom led dosing being shown as a large block accompanied by a statement of the dosing range for Symbicort, and with stable dosing being shown as a single line accompanied by a statement of the consistent dosing for Seretide.

- The leavepiece explicitly stated that in the Symbicort arm the steroid dose could only be increased according to symptoms. This was reinforced in the study design pictorial where the statement concerning symptom led dosing was asterisked to a footnote '1 inhalation bd stepped down to 1 od if controlled and temporarily stepped up to 4 bd for 7-14 days as needed according to symptoms'. As this was a well constructed study in line with the Symbicort SPC and AstraZeneca promotion, GlaxoSmithKline did not agree that this approach predetermined a higher symptom level in this group. It was not known prior to this study whether a stable dosing approach that addressed underlying inflammation over a longer period of time actually resulted in lower symptoms when compared to a reactive approach that adjusted treatment in response to individual symptoms. If the flexible dosing achieved the aim of controlling underlying inflammation then it was possible that more symptoms would have been recorded in the stable dosing arm of the trial. Clinical trials were conducted to answer such questions.

- AstraZeneca's reference to 82% of patients being stepped down to the lowest licensed dose of Symbicort, reflected the control achieved at higher doses. The value of 82% however was a cumulative value and reflected the number of patients who received the lowest dose at any time during the study. It was not a true reflection of overall levels of Symbicort use throughout the study.

- The leavepiece reflected the balance of evidence as it referred to the only randomised controlled trial that had compared the two different treatment approaches which were promoted by the two companies, stable dosing and symptom led dosing. By definition symptom led dosing would lead to variations in dosing within individuals over time, whereas stable dosing would provide longer time consistent dosing. It was unreasonable to expect that pharmacologically comparable steroid doses would be delivered to patients, but this design of study allowed the comparison of clinically relevant therapeutic pathways. It was therefore appropriate to provide evidence for physicians of any differences in the efficacies of these different dosing strategies when used in the clinical setting which might come about because of these different steroid doses received. The SUND study would not provide clinicians with this evidence since it compared pharmacologically equivalent steroid doses with the two products Seretide and Symbicort. The data from SUND provided no evidence on the clinical effect of the Symbicort symptom led adjustable maintenance dosing strategy, widely promoted by AstraZeneca, and might actually provide a misleading picture of the effect of Symbicort as promoted by AstraZeneca since the data represented the effect of a stable dosing strategy. Furthermore as an open-label study which did not reach significance in its primary end-point SUND did not add to the weight of evidence when compared against the robust design of the CONCEPT study, a randomised, double-dummy, placebo-controlled study which reached significance in its primary end-point.

Study design and relative inhaled steroid dose chosen

GlaxoSmithKline acknowledged that the design of the CONCEPT study and specifically the relative doses of inhaled corticosteroid were important issues for the understanding of the CONCEPT results. However AstraZeneca's understanding of the study was fundamentally flawed.

AstraZeneca had correctly noted that during the initial 4 week stabilisation phase patients remained on Seretide 250mcg 1 inhalation bd or Symbicort 200mcg 2 inhalation bd, an approximately equivalent dose of steroid, and during the variable maintenance phase of the trial patients in the Seretide arm remained fixed on Seretide 250mcg 1 inhalation bd whereas patients in the Symbicort arm were instructed to adjust their therapy according to symptoms.

However, Symbicort patients adjusted their dose according to a pre-defined treatment plan and stepped up or stepped down treatment according to the presence or absence of symptoms in accordance with the Symbicort SPC. Furthermore, the step up and step down criteria defined in the patient action plan accurately reflected guidance that had been provided by AstraZeneca to physicians for the use of Symbicort in their symptom led adjustable maintenance dosing strategy and product monograph:

- the AstraZeneca 'dose wheel' physicians' leavepiece clearly showed that a dose of 1 inhalation once daily had been recommended by AstraZeneca. In addition the step down and step up criteria on the dose wheel showed that the criteria set in the CONCEPT trial for step up and step down of Symbicort treatment were almost identical:
  - Step down in the AstraZeneca dose wheel was indicated when patients on 2 consecutive days needed no more than 1 puff of reliever medicine and had no night-time awakenings, and in the CONCEPT trial was indicated when patients had 2 consecutive days with no rescue medication use, no night-time awakenings and morning PEF at least 85% of baseline
  - Step up in the AstraZeneca dose wheel was indicated when patients on 2 consecutive days used more reliever than normal or had night-time awakenings, and in the CONCEPT trial was indicated when patients had 2 consecutive days with rescue medication used 3 or more times per day or night-time awakenings or morning PEF less than 85% of baseline

- the AstraZeneca product monograph from 2001 clearly showed the use of a dose of 2 inhalations twice a day initially to control symptoms and then reduction to 1 inhalation twice a day when symptom control had been achieved with subsequent step-up to 4 inhalations twice a day and step down to 1 inhalation twice a day according to symptoms and the possible reduction to 1 inhalation once a day if symptoms were sufficiently well controlled. This product monograph formed the basis for the dosage adopted for Symbicort in the CONCEPT trial and corresponded exactly to the dosage regime recommended by AstraZeneca for patients at the time the CONCEPT study was initiated.

AstraZeneca also stated that 'the majority of patients were instructed to down titrate to the lowest possible maintenance dose of inhaled steroid and remain on this dose until they developed symptoms'. This suggested that there was active involvement by investigators to push patients down to lower doses of Symbicort. This was not the case as patients followed a pre-defined action plan based on AstraZeneca's own materials, where adjustments in dose were made according to symptoms, reflecting the real clinical situation for patients if they were following the symptom led adjustable maintenance dosing strategy endorsed and promoted by AstraZeneca for Symbicort. The percentage of patients who stepped down to the lowest dose simply reflected the degree of control they and their supervising physicians (since a patient could not step down without the endorsement of an investigator) felt had been achieved using Symbicort in a symptom led adjustable maintenance dosing approach using step up and step down criteria in accordance with those recommended by AstraZeneca.

GlaxoSmithKline also noted that AstraZeneca had stated that in the CONCEPT study the dose for dose steroid comparison was unfair. As stated above, it was not the objective of this trial to compare like-for-like doses of the two steroids. The objective was to compare two treatment approaches, stable dosing versus symptom led dosing, the latter of which, by its very definition, would result in variable amounts of treatment being received. Consequently, no steroid dose was 'chosen' for this study, rather the steroid dose received in the Symbicort arm was a **result** of the trial, and indicated what might occur in patients in the clinical setting if the symptom led adjustable maintenance dosing approach was used. It was appropriate to undertake this trial as the symptom led adjustable maintenance dosing approach was the treatment strategy endorsed and promoted by AstraZeneca for Symbicort, and clinicians should know about the clinical outcome of using Symbicort in this way to help guide them as to the selection of the appropriate dosing strategy for their patients.

Comparative SPC dosing recommendations

GlaxoSmithKline noted that AstraZeneca had correctly pointed out the respective SPC dosing recommendations of both Symbicort and Seretide, and the fact that the CONCEPT study did not allow well controlled Seretide patients to step down to once daily dosing, an option included in the Seretide SPC.

However, the design of the CONCEPT study did not require Seretide patients to step down to once daily dosing as this was **not** part of the treatment approach that GlaxoSmithKline had adopted for the use of Seretide. The treatment strategy for Seretide, based on the GOAL study, and investigated in the CONCEPT study was fixed stable dosing with Seretide for a prolonged period to control underlying inflammation, not symptom led adjustable dosing. It was known that control of underlying inflammation required long term treatment, possibly for as long as a year in the context of bronchial hyper-responsiveness (Woolcock 2001), and the GlaxoSmithKline treatment strategy was based on addressing this underlying problem. Therefore it was appropriate that Seretide treatment was not stepped down during the year-long period of the trial since within this time frame GlaxoSmithKline considered that patients would not have gained control of their underlying inflammation and therefore symptoms. The evidence clearly showed that long-term treatment was needed to control symptoms such as bronchial hyper-responsiveness. Consequently, it would only be after the period of this trial that patients would have gained control of all their symptoms and therefore be appropriate for consideration of step down of their treatment as suggested in the SPC.

In contrast, the treatment approach for Symbicort, as promoted and endorsed by AstraZeneca, required adjustment of treatment by patients in the short-term in response to more obvious symptoms such as coughing, wheezing and peak flow. It was known that control of these symptoms could be gained much more quickly than other less obvious symptoms such as bronchial hyper-responsiveness (Woolcock), therefore it was appropriate that short-term treatment changes were made for Symbicort as recommended in its SPC and in accordance with the promotional guidance provided by AstraZeneca.

The Code required promotion to be within the SPC, but did not require that promotion followed the entirety of the SPC. It was therefore not misleading to promote a study which investigated some, but not all of the individual aspects of the SPC indication and dosing statements. It would be unrealistic to expect every study to reflect every aspect of the SPC. The leavepiece clearly detailed the study design and the dosages of Seretide and Symbicort that were used as well as what dose adjustments were made. All of these doses were consistent with the SPCs for the two products and the different treatment regimens were clearly set out for the reader.

Contradicts the balance of evidence supporting adjustable maintenance dosing vs fixed dosing

GlaxoSmithKline acknowledged that AstraZeneca had conducted studies involving over 10,000 patients in 8 trials using Symbicort in a symptom led adjustable maintenance dosing regime, and in these trials patients were able to step down to a minimum dosage of 2 inhalations twice a day. However, to compare non comparative studies with different designs might be misleading, and although AstraZeneca studies had shown this, this minimum dosing recommendation was not in accordance with the Symbicort SPC and

AstraZeneca's own dosing recommendations which included a dose of 1 inhalation once a day. Furthermore all of these trials used an open-label design which, in contrast to the extremely robust randomised, double-blind, double-dummy controlled design of the CONCEPT study, were known to be open to potential bias from investigators and patients, and were of a much shorter duration than the CONCEPT trial. (In contrast to the CONCEPT trial which lasted 52 weeks, the AstraZeneca trials included four trials of 3 months, one of 4 months and three which lasted 6 months.) Consequently, it was appropriate that the CONCEPT study was considered as the only robustly designed long-term trial which provided level 1 evidence of the comparison between fixed dosing and symptom led adjustable maintenance dosing, and included the appropriate minimum dosage as recommended by AstraZeneca in its promotional materials.

GlaxoSmithKline noted that NICE and other such review bodies only considered level 1 (randomised study) evidence. GlaxoSmithKline's position with this leavepiece was thus consistent with well accepted principles.

GlaxoSmithKline disagreed with AstraZeneca's statement that the SUND study provided a comparison of a 'fairer' overall dose of inhaled corticosteroid; in the SUND study the minimum inhaled dose of Symbicort was 2 inhalations per day, not 1 as in CONCEPT, and this did not reflect the treatment recommendations for physicians which clearly included a dose of 1 inhalation once a day. Furthermore, once again AstraZeneca had not considered that SUND was a 6 month open-label study open to potential bias from investigators and patients, that failed to achieve its primary end point. AstraZeneca had defended this design due to the 'practicable difficulties for patients in using a double-dummy study design' for such a trial. However, the CONCEPT study demonstrated that these problems could be overcome and a much more robust randomised, double-blind, double-dummy controlled trial could be performed in asthmatic patients to more appropriately determine the effects of two different treatment approaches. GlaxoSmithKline did not agree that SUND demonstrated that Symbicort adjustable maintenance dosing was equivalent in terms of achieving the primary end-point of odds of achieving a well-controlled asthma week when compared to fixed dose Seretide as this study was not designed as an equivalence study. The design of the SUND study, and numbers of patients involved, clearly indicated that it was set up as a superiority study to investigate whether Symbicort was better than Seretide at achieving a well-controlled asthma week. In not achieving any significant difference in its primary end-point SUND only showed that Symbicort was not superior to Seretide in achieving a well-controlled asthma week. However, equivalence could not be inferred from this result and AstraZeneca was wrong to suggest that it could.

Consequently, GlaxoSmithKline did not agree that these trials showed adjustable maintenance dosing to be more efficacious than fixed dose therapy. The difference between these was not an issue of 'appropriate comparison doses' more an issue of study design, since the evidence from open-label short-term trials could not be compared with evidence from randomised, double-blind, double-dummy, controlled trials looking at long-term outcomes.

GlaxoSmithKline stated that it was inappropriate for it to comment on the article by Murphy other than to say that the other studies referred to in the article had also been raised by AstraZeneca in its complaint. GlaxoSmithKline's response to this was detailed above.

AstraZeneca had also quoted recent prescribing data to indicate that in normal clinical practice only a small minority of patients were instructed by their health professional to take Symbicort 1 inhalation once daily. GlaxoSmithKline failed to see the relevance of this point in a complaint about a well designed clinical study that robustly examined the two companies' treatment approaches and would inform clinical practice to a much greater extent than prescribing data.

It was not the objective of the CONCEPT study, as already stated, to compare clinical practice but to compare the two treatment approaches recommended by the two companies in a randomised, double-dummy, double-blind, controlled trial looking at long-term clinical outcomes. CONCEPT was the only trial that offered robust evidence for clinicians of the comparison between fixed dosing and symptom led dosing strategies.

Specific points

GlaxoSmithKline did not believe that the CONCEPT leavepiece was misleading or that it presented an inaccurate, unfair or unbalanced representation of the available evidence, since CONCEPT was designed to compare two treatment approaches, not pharmacologically comparable steroid dosing; it was the only long-term robustly designed clinical trial investigating this question. Furthermore, CONCEPT used dosing strategies for Seretide and Symbicort as recommended for health professionals in promotional materials.

1 'A comparison of two treatment approaches for asthma'

The study design in the leavepiece illustrated the different stages and dosing regimes used in the trial appropriately. However, it did not show that 82% of patients were stepped down to 1 inhalation once a day. GlaxoSmithKline believed that this piece of information was in itself misleading since 82% of patients were actually stepped down to 1 inhalation once a day at some point during the trial. What the figure of 82% did not convey was how long patients actually spent at this dosage level, and that if patients stepped down to 1 inhalation once a day but then subsequently had an increase in symptoms or an exacerbation such that they had to step up their treatment they were not allowed to step back down to a dose of 1 inhalation once a day at any further point during the trial. Consequently, GlaxoSmithKline did not consider that including the percentage of patients in the Symbicort arm that stepped down to 1

inhalation once a day would be helpful as it raised more questions than it answered and in itself could actually mislead health professionals into thinking that patients stepped down and remained at that dose.

The page complained about by AstraZeneca fully and faithfully represented the design of the study and reflected the ability of patients to down titrate to doses compatible with the Symbicort SPC and in line with AstraZeneca's promotional strategy. As such GlaxoSmithKline refuted any breach of Clauses 7.2 or 7.3.

2 'Seretide stable dosing achieves superior asthma control compared to formoterol/ budesonide symptom led dosing'

GlaxoSmithKline considered that this claim was an accurate, fair and objective summary of all the available evidence and was not exaggerated or misleading since all the conflicting evidence for the efficacy of Symbicort had been gained from short-term open-label trials that were open to considerable bias and did not provide sufficient weight of evidence to challenge the data gained from a long-term robustly designed randomised, double-blind, double-dummy, controlled trial such as CONCEPT.

CONCEPT was the only study that examined the two different dosing strategies of the individual products as promoted by the individual companies. The design of CONCEPT was such as to investigate the effects of two different treatment approaches, not pharmacologically comparable steroid dosing, which would provide evidence to health professionals of the clinical outcomes that would be seen in patients for each of these treatment strategies. By its very nature, symptom led adjustable maintenance dosing resulted in variable dosing in individual patients and the corticosteroid dosage received by patients in this arm of the trial was actually a result of this treatment approach not a pre-determined factor defined in the protocol. The data from CONCEPT were extremely important for health professionals such that they provided further knowledge of the clinical efficacy of a fixed dosing approach compared with an adjustable dosing approach as recommended by AstraZeneca.

AstraZeneca's assertion that the details of the dosages used for symptom led adjustable maintenance dosing in current clinical practice did not reflect entirely those used in the CONCEPT trial were surprising since the dosage regime used in CONCEPT was based on that recommended by AstraZeneca itself.

In conclusion, GlaxoSmithKline did not consider that the promotional use of the CONCEPT study represented any breach of the Code.

PANEL RULING

The Panel noted that CONCEPT was a comparative study of two different treatment approaches for asthma – fixed maintenance dosing with Seretide or adjustable maintenance dosing with Symbicort. Patients in the study were previously symptomatic on either 200-500mcg inhaled corticosteroid plus long acting $beta_2$ agonist or >500-1000mcg inhaled corticosteroid alone. Patients were initially stabilized, over four weeks, on Seretide 250 1 puff twice daily (total daily dose (tdd) salmeterol 100mcg/fluticasone 500mcg) or Symbicort 2 puffs twice daily (tdd formeterol 24mcg/budesonide 800mcg twice daily). During this stabilization phase, when both groups received fixed doses, the percentage of symptom-free days was similar between the two treatments. Having been stabilized over 4 weeks, patients in the Symbicort group were instructed to halve their dose to 1 puff twice daily (tdd formoterol 12mcg/budesonide 400mcg). At subsequent clinic visits patients who continued to be controlled could halve the dose again to 1 puff daily (formoterol 6mcg/budesonide 200mcg daily). Such low dosing was not inconsistent with the Symbicort SPC. If after stepping down to this lowest dose patients subsequently lost control of their asthma, as defined by certain criteria, they were instructed to go back to not less than 1 puff twice daily (tdd formoterol 12mcg/budesonide 400mcg) throughout the rest of the 52 week period. The study was not a comparison of steroid dose *per se*.

During the course of the study 83.1% of patients in the Symbicort group stepped down their dose to 1 puff daily at some time and 41.6% increased their dose to 4 puffs twice daily for 7-14 days at least once. Over the 52 week treatment period the mean daily dose of fluticasone (from Seretide two puffs daily) was 463mcg and the mean daily dose of budesonide (from adjustable dosing of Symbicort) was 480mcg. Diary card data showed that Symbicort patients used a mean of 1.8 inhalations daily (equivalent to 360mcg budesonide).

The Panel noted that the leavepiece did not detail the mean daily dose of product or the mean daily number of inhalations. Further the leavepiece gave no details as to how patients, in practice, had adjusted the dose of Symbicort. It was thus difficult for readers to fully understand the clinical significance of the results. The Panel considered that in this regard the leavepiece was misleading. Breaches of Clauses 7.2 and 7.3 were ruled.

The Panel noted AstraZeneca's comments regarding the design of the CONCEPT study, the fact that its results seemed to contradict other studies and that the symptom led dosing approach used was not one that was routinely used in clinical practice. However, other studies had been open-label as opposed to the CONCEPT study which was double-blind. Additionally the CONCEPT study had allowed Symbicort to be dosed at 1 puff daily which, although lower than in other studies, was nonetheless consistent with the Symbicort SPC. In that regard, whilst noting its ruling above, the Panel did not consider that claims such as 'Seretide stable dosing achieves superior asthma control compared to formoterol/budesonide symptom led dosing' regarding the symptom led dosing of Symbicort *per se* were misleading. No breach of Clauses 7.2 and 7.3 was ruled.

Complaint received **8 May 2006**

Case completed **25 July 2006**