CASE AUTH/2570/12/12

GLAXOSMITHKLINE v NAPP

Flutiform leavepieces

GlaxoSmithKline complained about two Flutiform (fluticasone/formoterol) leavepieces issued by Napp. GlaxoSmithKline marketed Seretide (fluticasone/salmeterol). Flutiform and Seretide were both indicated for the treatment of asthma. The leavepieces included a comparison of Flutiform pressurized metered dose inhaler (pMDI) with Serotide Evohaler (pMDI).

The response from Napp is detailed below.

GlaxoSmithKline alleged that the claim 'Comparable clinical efficacy' (between Seretide and Flutiform) did not reflect the evidence and misled the reader. The claim was based upon a 12 week, open label study using low and medium doses of both products in patients aged 18 years or older (Bodzenta-Lukaszyk *et al* 2011). The study demonstrated non-inferiority of forced expiratory volume in the first second (FEV1) as a primary outcome and discontinuation due to lack of efficacy as a secondary outcome. GlaxoSmithKline submitted that the study did not support the claim.

The Panel noted that the primary endpoint of Bodzenta-Lukaszyk *et al* was non-inferiority based on mean FEV1. Secondary endpoints included discontinuations due to lack of efficacy, time to onset of action, peak expiratory flow rates and other lung function parameters, amount of rescue medication use, asthma symptom scores, sleep disturbance due to asthma, daily corticosteroid doses and asthma exacerbations. The study demonstrated that Flutiform was comparable to Seretide in terms of the primary endpoint and certain secondary efficacy endpoints. Flutiform was superior to Seretide in terms of time to onset of action.

Whilst noting that FEV1 was a fundamental efficacy measurement, the Panel considered the broad unqualified claim 'comparable efficacy' implied more than a measurement of FEV1. In this regard the Panel noted that the secondary outcome data in Bodzenta-Lukaszyk *et al* (2011a) showed that Flutiform and Seretide were similar in a number of additional relevant efficacy measurements.

The Panel noted that Flutiform was not recommended for use in children younger than 12 and that high dose Flutiform should not be used in adolescents. Seretide 25/50mcg, however, could be prescribed from the age of 4 and from the age of 12 children could be treated with all three doses of Seretide.

The Panel noted that the heading to the page at issue in leavepiece 1 read 'Why should I prescribe Flutiform instead of Seretide Evohaler?' The Panel considered that many readers would already be familiar with the Seretide Evohaler. The Panel considered that the broad, unqualified claim 'Comparable clinical efficacy' implied that Flutiform could be used in all of those patients for whom Seretide might be prescribed and that there was robust comparative clinical data in relation to all doses and patient populations and that was not so. The Panel noted that there was some comparative efficacy data but considered that insufficient information about the study had been provided to enable the reader to accurately interpret the claim which was consequently misleading and incapable of substantiation. The Panel noted that the first page of the leavepiece stated that Flutiform was 'combined for the first time for asthma maintenance therapy for patients 12 years and older (low and medium strengths); adults (all strengths)'. However, this statement was in a small font size such that, in the Panel's view, it would be missed by many readers. The Panel did not consider that the statement was prominent enough to set the rest of the leavepiece in context. In the Panel's view the statement on the first page did not negate the otherwise misleading impression given by the claim 'Comparable clinical efficacy'. Breaches of the Code were ruled.

The Panel noted that in leavepiece 2 a preceding bullet point explained that Flutiform 50/5mcg and 125/5mcg were licensed for use in patients aged 12 years and above. The immediate subheading to the claim in question made it clear that patients had mild to moderate-severe persistent asthma. However, it had not been made clear that only medium and low doses of Seretide Evohaler had been compared in patients aged 18 years or over. The Panel also noted its comments above about the secondary clinical endpoints in Bodzenta-Lukaszyk *et al*. On balance, the Panel considered that the rulings made in relation to leavepiece 1 also applied to leavepiece 2; further breaches of the Code were ruled.

GlaxoSmithKline alleged that the cited reference (Mansur 2008 published in full as Mansur and Kaiser 2012) did not support the claim 'The efficacy and tolerability of Flutiform were sustained for up to 12 months'. The positioning of the claim directly below the claim for comparable efficacy misled readers into assuming that 'comparable efficacy' had been demonstrated over 12 months.

The Panel noted that Mansur and Kaiser was an open label study in which mild to moderate-severe asthmatics age 12 years and over were treated twice daily with low or medium dose Flutiform for 6 or 12 months. The primary and secondary objectives were the long-term safety and efficacy of Flutiform.

The study demonstrated statistically significant improvements overall and for both treatment groups for each efficacy assessment. Flutiform demonstrated a good safety and efficacy profile over the 12 month study period.

The Panel noted that the claim 'The efficacy and tolerability of Flutiform were sustained for up to 12 months' appeared immediately beneath the claim for comparable clinical efficacy with Seretide. The Panel considered that the positioning of the claims was such that the second would inevitably be read in light of the first and thus readers would infer that comparable clinical efficacy with Seretide was demonstrated for up to 12 months and that was not so. The claim was misleading on this point as alleged and a breach of the Code was ruled.

GlaxoSmithKline noted the question 'Why should I prescribe flutiform instead of Seretide Evohaler' and submitted that Flutiform was not a suitable substitute for all patients who were eligible for Seretide. Seretide 50 Evohaler was licensed from 4 years and older whilst Seretide 125 and 250 Evohalers were licensed from age 12 years and older. Flutiform 50 and 125 were licensed from 12 years and older and Flutiform 250 was licensed from age 18 years and older. Unlike Seretide, Flutiform contained ethanol and was only licensed for use with the AeroChamber Plus spacer device; Seretide was licensed for use with both the Volumatic and AeroChamber Plus spacer devices.

GlaxoSmithKline alleged that the omission of clinically important differences when advising that Flutiform was an alternative to Seretide was misleading; it was not fair, balanced or objective and created confusion between the two products. Prescribers were not informed of the unsuitability of Flutiform for some patients prescribed Seretide. This might encourage off-label prescribing and usage and compromise patient safety.

The Panel noted that Flutiform was not a suitable substitute for younger patients who could be treated with Seretide Evohaler. The Panel again noted that many readers would already be familiar with Seretide. The Panel considered that in the absence of information to the contrary, readers would assume that Flutiform could be substituted for Seretide Evohaler in all circumstances and that was not so. The information about Flutiform's licensed indication, in relatively small print, was insufficient to negate the unequivocal impression given by the claim. The Panel considered that the claim was misleading and could not be substantiated. Breaches of the Code were ruled.

GlaxoSmithKline stated that although 'Faster onset of action' was presented as the key differentiator between Flutiform and Seretide Evohaler it had not been established that a shorter time to onset of action was of value in a controller medicine. Furthermore, Napp did not provide any clinical evidence to substantiate the clinical relevance of the claim.

GlaxoSmithKline noted that in leavepiece 1 the claim 'Faster onset of action' appeared on the same page and next to the bold claim 'flutiform is licensed for maintenance therapy and not for acute symptom relief'. A claim for a faster onset of action was typically synonymous with a reliever (or SMART [Symbicort Maintenance and Reliever Therapy] therapy) and could, potentially, lead to inappropriate off-label use of Flutiform inconsistent with its SPC and compromise patient safety.

GlaxoSmithKline maintained that Napp had failed to substantiate the clinical relevance of the claim or give information such that readers could assess the clinical relevance of a faster onset of action with this controller medication. The juxtaposition of claims in leavepiece 1 misled the reader and potentially encouraged Flutiform to be misused and prescribed off-licence.

The Panel noted both parties' submissions about the clinical relevance of the claim. In particular, the Panel noted the studies submitted by Napp indicated overall that onset of action was of clinical interest and relevance for a maintenance therapy. The claim was not misleading or incapable of substantiation on this point. No breach of the Code was ruled.

The Panel noted that alongside the bullet points, including that at issue above, was an image of a Flutiform pMDI beneath which was the prominent claim 'flutiform is licensed for maintenance therapy and not for acute symptom relief'. The Panel did not consider that the juxtaposing of the claim 'Faster onset of action' and the description of its licensed use for maintenance therapy misled the reader as alleged or promoted it in a manner that was inconsistent with its marketing authorization. It was clear that Flutiform was licensed for maintenance therapy. The Panel further noted that the claim was within the context of 'Why should I prescribe flutiform instead of Seretide Evohaler?'. The Panel again noted that prescribers would be familiar with Seretide and know that it was only indicated as a maintenance therapy. No breach of the Code was ruled.

GlaxoSmithKline stated that the data cited in support of claims for cost-effectiveness most closely resembled a cost-minimisation analysis which required robust evidence for clinical equivalence with respect to patient outcomes. There was, however, no randomised, double-blind head-to-head study which compared Seretide and Flutiform. The only comparison between the two was Bodzenta-Lukaszyk *et al* and, as noted above, the primary endpoint of the trial was non-inferiority of FEV1. High doses of Seretide and Flutiform had not been compared and studies of high dose were an essential prerequisite to establish comparable safety with any degree of certainty.

GlaxoSmithKline alleged that the cost-effectiveness claims were not fair, accurate or balanced and that

the cost comparisons made were misleading and not substantiated by the cited reference.

The Panel noted that the claims at issue were referenced to data on file which Napp described as a cost-minimisation study. Only acquisition costs were compared. The Panel noted each party's submission on whether Bodzenta-Lukaszyk *et al* demonstrated comparable efficacy and thus whether a cost-minimisation study was the appropriate analysis. In particular, the Panel noted the study was a non-inferiority study and had not been designed to demonstrate equivalence. The Panel also noted its rulings and comments above about the study in relation to patients' ages, doses and asthma severity. The Panel queried whether a cost-minimisation analysis was therefore appropriate.

The Panel noted that cost-minimisation studies were a legitimate activity; any claims derived therefrom had to clearly reflect the analysis and not otherwise be misleading. The Panel considered that a reader would expect the claim 'cost-effectiveness' in the absence of further qualification, to mean more than a simple comparison of acquisition costs. In each leavepiece subsequent and distinct sections discussed comparative acquisition costs thus compounding the impression that 'cost-effectiveness' was different and broader than a simple cost comparison.

The Panel considered that the claims 'Improved cost-effectiveness' in leavepiece 1, '… a cost-effective treatment for asthma management' and '… a cost-effective treatment choice …' in leavepiece 2, each implied that matters broader than acquisition cost had been compared. In addition the Panel noted its concerns about the cost-minimisation study and its reliance on Bodzenta-Lukaszyk *et al* as set out above. The claims were thus each misleading and incapable of substantiation. Breaches of the Code were ruled.

GlaxoSmithKline noted the claims 'cost-effective treatment for asthma management' and 'a cost-effective treatment choice when ICS/LABA [inhaled corticosteroid/long-acting B2-agonist] combination inhalers were being considered at Step 3 or 4 of the SIGN/BTS [Scottish Intercollegiate Guidelines Network/British Thoracic Society] guidelines'. Napp data on file was cited in support of both claims. GlaxoSmithKline submitted that there were other products and devices available for 'asthma management' and at 'Step 3 or 4 of the BTS/SIGN guidelines'. These had not been included within the leavepiece or within the Napp data on file. Some of these products cost less than Flutiform.

GlaxoSmithKline submitted that the leavepiece advised switching. Switching inhalers was a complex process and required follow-up of the patient to ensure asthma control was maintained and that the patient continued to use the inhaler properly.

No evidence was presented in the leavepiece to demonstrate that asthma control was maintained when/if patients were switched. Consequently the claims for potential annual savings did not take into account the costs associated with the necessary additional clinical interactions required with patients when they had their medicines changed or the potential costs associated with the risk of any resultant exacerbations.

In addition, the data presented were stratified by age; however, there were many patients who could not be switched to Flutiform who had not been considered eg patients who used a Volumatic spacer or those who were unable to use inhalers containing ethanol. Furthermore, the Napp data on file did not include the full range of products and devices and thus could not substantiate the above claims.

The Panel noted that the heading of leavepiece 2 was a broad unqualified claim that Flutiform was a cost-effective treatment for asthma management when compared with all other relevant products. The comparison was not limited to that with Seretide Evohaler. The Panel noted its general comments above. The Panel considered that the heading was misleading as alleged and a breach of the Code was ruled.

The Panel noted that the claim 'flutiform provides the clinician with a cost-effective treatment choice when ICS/LABA combination inhalers are being considered at Step 3 or 4 of the SIGN/BTS guidelines' was the sole bullet point in a section headed 'Rationale for flutiform'. In the Panel's view the claim implied that Flutiform was a cost-effective choice when compared with all other ICS/LABA combination inhalers used at Steps 3 or 4 of the guidelines. It was not limited to a comparison with the Seretide Evohaler as alleged and was misleading in this regard. Breaches of the Code were ruled.

The Panel noted that the table within the section headed 'Potential savings per annum' compared the cost savings, based on acquisition costs if 25%, 50% or 75% of patients on Seretide Evohaler 50, 125 and 250 were switched to Flutiform. In the Panel's view the table did not advocate switching *per se* as alleged by GlaxoSmithKline. It merely set out the potential savings based on acquisition costs in the event of a switch to the Seretide Evohaler. In the Panel's view, the basis of the comparison was clear and was not misleading. No breach of the Code was ruled.

GlaxoSmithKline stated that in leavepiece 1 a claim of cost-effectiveness lay adjacent to a cost comparison of the three different strengths of Seretide Evohaler and Flutiform. Cost-effectiveness compared with Evohaler had not been demonstrated as discussed above. Given that cost-effectiveness had not been demonstrated, the juxtapositioning of this statement next to a cost comparison table that was itself not balanced, was misleading.

The cost comparison table only compared Flutiform to Evohaler. GlaxoSmithKline noted that alternative maintenance therapies were available at Step 3 and 4 of the BTS/SIGN guidelines. Furthermore, the

omission by Napp of the Seretide Accuhaler prices, particularly the high strength, appeared deliberate to conceal the fact that the Seretide 500 Accuhaler was less expensive than Flutiform 250/10mcg. In inter-company dialogue, Napp submitted that the Seretide Evohaler was the most appropriate comparator because clinical data vs Seretide Evohaler had been presented within leavepiece 1. GlaxoSmithKline disagreed with Napp's position and noted that the appropriate information referenced to Bodzenta-Lukaszyk *et al*, for the mid/ low doses comparisons was missing from the cost comparison table. By so doing, the reader was unaware that the rationale for this cost comparison was based solely upon non-inferior FEV1 results over a 12 week period in adults.

Whilst GlaxoSmithKline acknowledged that Napp's rationale for only directly comparing the two products, when other products were available, was because head-to-head data existed, it must be clearly acknowledged that data only existed for the low and medium doses of the inhaler, in 18 year olds and in an open label study that did not include severe patients.

As previously highlighted, Seretide Evohaler and Flutiform differed in many aspects; licensed age ranges, alcohol content and spacer device usage. None of these had been made clear within leavepiece 1 which implied that all patients could be prescribed Flutiform instead of Seretide Evohaler. Clearly, this was not the case and Napp was obliged to present these important differences in a fully transparent and balanced way.

In summary, GlaxoSmithKline alleged that the cost comparison table was misleading, not accurate, fair or balanced.

The Panel noted its rulings above in relation to the claim 'Improved cost-effectiveness'. That claim was a bullet point beneath a prominent subheading and page heading. It was not 'next to' the cost comparison table on the facing page as GlaxoSmithKline alleged, nor was it within that table's immediate visual field. The Panel, whilst noting its ruling above, did not consider that the position of the claim 'Improved cost-effectiveness' on page 1 in relation to the table on page 2 was, in itself, misleading as alleged. No breach of the Code was ruled.

The Panel considered that the basis of the comparison in the table was clear, the acquisition costs of the three strengths of flutiform were compared with those of the three strengths of Seretide Evohaler. There was no implication that all patients could be prescribed Flutiform instead of Seretide Evohaler, as alleged. Nor was it unacceptable to directly compare the acquisition costs of products if the basis of that comparison was abundantly clear. The table was not misleading as alleged. No breach of the Code was ruled.

GlaxoSmithKline stated that the leavepiece compared both clinical and economic aspects of Seretide Evohaler and Flutiform. The claim, 'flutiform has a simple dosing schedule administered as 2 puffs, twice daily', appeared directly below the table at issue above.

In a comparative leavepiece designed to state why Flutiform should be prescribed instead of Seretide, the juxtaposition of the above statement directly below a comparative table implied that Seretide's dosing schedule was not simple or not as simple as Flutiform. This was not the case as the dosing schedules for the two inhalers were exactly the same.

To describe a dosing schedule as 'simple' was both promotional and a hanging comparison and therefore required substantiation. Alternative, simpler dosing schedules for asthma were available eg Seretide Accuhaler, one puff twice a day. Napp did not provide evidence to demonstrate that patients viewed a dosing schedule of two puffs twice a day as being simple but, in inter-company dialogue, advised that 'It ... is a plain statement of fact in terms of the dosing schedule for Flutiform being simple'.

GlaxoSmithKline alleged that within comparative tables and leavepieces between Seretide and Flutiform, claims of a simple dosing schedule for Flutiform when the dosing schedules were the same was misleading. Furthermore, when simpler dosing schedules were available, a claim of simple was not accurate or balanced and was misleading.

The Panel noted that the claim in question appeared in small print beneath the comparative table at issue above which comprised most of the page. The Panel considered that the claim would be considered by readers in the context of the overall comparative message of the page and thus it implied that Seretide Evohaler did not have a simple dosing schedule and that was not so. Seretide Evohaler had the same dosing schedule as Flutiform. The claim was misleading in this regard and incapable of substantiation. Breaches of the Code were ruled.

The Panel considered that the claim indirectly compared the dosing schedule of Flutiform with Seretide Evohaler. The Panel therefore did not consider the claim was a hanging comparison as alleged. Nor was it misleading because other products with simpler dosing schedules were available as alleged by GlaxoSmithKline. The Panel considered that the claim in question was not misleading on these points and no breach of the Code was ruled.

GlaxoSmithKline submitted, given the totality of the multiple issues raised and unresolved through extensive inter-company dialogue, that collectively the two leavepieces disparaged Seretide. In addition, given the seriousness and number of breaches, the failure to maintain high standards and the potential to encourage Flutiform prescribing outside the marketing authorization and impact upon patient safety, the two leavepieces constituted additional breaches of the Code including Clause 2.

The Panel noted its rulings above of breaches and no breaches of the Code. Whilst some comparisons had been considered misleading, the Panel did not

consider that they went beyond that and disparaged Seretide Evohaler. No breach of the Code was ruled.

The Panel noted its rulings of breaches of the Code set out above and considered that high standards had not been maintained. A breach of the Code was ruled.

Although noting its rulings above, the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was reserved to indicate particular disapproval of a company's material or activities. No breach of Clause 2 was ruled.

GlaxoSmithKline appealed the ruling of no breach of Clause 2. The company subsequently tried to withdraw its appeal but was prevented from doing so by the Constitution and Procedure. The Appeal Board noted that the Panel had ruled a breach of the Code in that high standards had not been maintained. The Appeal Board was concerned about the breaches of the Code and the possible, theoretical adverse consequences of some of the claims on patient safety but considered that, on balance, the circumstances did not warrant a breach of Clause 2 and it upheld the Panel's ruling of no breach of Clause 2. The appeal was thus unsuccessful.

GlaxoSmithKline UK Limited complained about two Flutiform (fluticasone propionate/formoterol) leavepieces issued by Napp Pharmaceuticals Limited which, *inter alia*, compared Flutiform with GlaxoSmithKline's product Seretide (fluticasone/salmeterol). Flutiform was a pressurised metered dose inhaler (pMDI) and the leavepieces compared Flutiform with Seretide Evohaler also a pMDI. Leavepiece 1 (ref UK/FLUT-11050) was a four page, A5 leaflet. The front page was headed with a search engine box 'Fluticasone and formoterol in a fixed-dose combination'. The search returned one result, depicted in the highlighted box below, 'Flutiform'. Leavepiece 2 (ref UK/FLUT-11023a) was a double sided, A4 document headed 'flutiform (fluticasone propionate/formoterol fumarate) inhaler as a cost-effective treatment for asthma management'.

Flutiform was indicated in the regular treatment of asthma where the use of a combination product (an inhaled corticosteroid [fluticasone] and a long-acting β_2-agonist [formoterol]) was appropriate. Seretide was similarly indicated in the regular treatment of asthma where the use of a combination product was appropriate.

Both parties provided extensive background information which is summarised below.

Summary of the background information provided by GlaxoSmithKline

GlaxoSmithKline explained that there were two main types of medicines to treat asthma: relievers and controllers.

Relievers contained a short-acting β_2-agonist (SABA), were used on an 'as required' basis to quickly relieve symptoms of an asthma exacerbation and reverse bronchoconstriction.

Controllers, which contained a combination of a long-acting β_2-agonist (LABA) and an inhaled corticosteroid (ICS), were used on a daily basis for the maintenance therapy of asthma so patients could achieve and maintain control of their symptoms. Seretide and Flutiform were both combination products.

Seretide was available in two different devices, a metered dose inhaler (MDI), the Evohaler and a dry powder inhaler, the Accuhaler. Flutiform was available only as a MDI.

GlaxoSmithKline explained that both Seretide and Flutiform were used at Steps 3 to 5 of the British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) Guidelines. The BTS/SIGN Guidelines defined the current standard of care in the UK and advised that the therapy goal was to achieve and maintain control. UK and international treatment guidelines stated that to demonstrate if asthma control was achieved in patients either in a clinical trial or within clinical practice, effective treatments must demonstrate that control of both lung function and clinical symptoms could be achieved. It was not appropriate to specify a single endpoint for the assessment of asthma control, and clinical efficacy studies should use endpoints which captured both lung function and clinical symptoms. GlaxoSmithKline provided a table of data summarising the parameters for asthma control as defined in various guidelines.

GlaxoSmithKline explained that the Gaining Optimal Asthma Control (GOAL) study (Bateman *et al* 2004) was a 1 year, stratified, randomised, double-blind, parallel-group study which compared the efficacy and safety of individual, pre-defined, stepwise increases of Seretide with Flixotide (fluticasone propionate, GlaxoSmithKline, monotherapy). Within the GOAL study Seretide achieved and maintained guideline defined control over 12 months. GlaxoSmithKline provided a table which compared the primary endpoints of the GOAL study, Bodzenta-Lukaszyk *et al* (2011a) and Bodzenta-Lukaszyk *et al* (2011b).

Currently there were no randomised, double-blind, head-to-head studies which compared Seretide Evohaler with Flutiform to investigate if asthma control as defined by UK and international guidelines could be achieved. The only comparative study was a 12 week, open label, non-inferiority study which investigated the low and mid doses of both Seretide Evohaler and Flutiform in adults over the age of 18 years, using a spacer device (Bodzenta-Lukaszyk *et al* 2011a). The primary outcome, ie non-inferiority of the forced expiratory volume in the first second (FEV1) over a 12 week period in the full analysis set, was demonstrated. Of the secondary outcomes, the study demonstrated non-inferiority of discontinuations of study medication, and Flutiform was seen to have a faster onset of action. The actual times to onset of action were not stated in the published paper although this difference diminished over the 12 week treatment period. The patients'

assessment of study medication significantly favoured Seretide (Odds ratio 0.495 CI 0.289, 0.848), and trends in favour of Seretide were seen for rescue medication use but this did not reach significance for the published per-protocol population. Importantly, this head-to-head study did not demonstrate non-inferiority between Flutiform and Seretide for any of the clinical measures of asthma control.

Bodzenta-Lukaszyk *et al* (2011a) did not include adolescents and the high doses were not compared. In addition, only less severe patients were included as evidenced by observed exacerbation rates of 14% over 12 weeks in patients taking Flutiform compared with exacerbation rates of 35.1% over 8 weeks seen when Flutiform was compared with its individual components (Bodzenta-Lukaszyk *et al* 2011b). In both studies, numerically more patients taking Flutiform experienced severe exacerbations than those patients taking Seretide or GlaxoSmithKline's fluticasone propionate monotherapy. The current head-to-head data were not of sufficient duration or adequately powered to determine whether this result might represent a discriminatory effect between the two products due to the difference in steroid bioavailability.

Hochhaus and Kaiser (2011) suggested that Flutiform delivered 24-31% less fluticasone to the lungs than GlaxoSmithKline fluticasone monotherapy. However, importantly, the relationship between the bioavailability of Seretide and Flutiform had not been studied. GlaxoSmithKline noted, when salmeterol and fluticasone propionate were administered in combination by the inhaled route, as Seretide, the pharmacokinetics of each component were similar to those observed when the medicines were administered separately. The absolute bioavailability of a single dose of inhaled fluticasone propionate in healthy subjects varied between approximately 5-11% of the nominal dose depending on the inhalation device used (Seretide Evohaler summary of product characteristics (SPC)).

Summary of the background information provided by Napp

Napp explained that Flutiform was a new fixed-dose, inhaled combination of two well-known and established active substances: the ICS fluticasone propionate and the LABA formoterol fumarate. Fluticasone was the ICS in GlaxoSmithKline's Seretide combination inhaler, whilst formoterol was the LABA in AstraZeneca's Symbicort and Chiesi's Fostair.

Fluticasone propionate and formoterol fumarate had also been available for many years as individual inhaled monotherapies. The efficacy and safety profile of fluticasone was well established; it was a highly effective maintenance treatment for asthma, both as a single inhaler therapy and as the ICS component of the fixed-dose combination Seretide. The efficacy and safety profile of formoterol was also well established. Formoterol provided significantly more rapid bronchodilation than salmeterol and was comparable to that of the SABA salbutamol.

Although fluticasone and formoterol were available as monotherapies and in other combinations, until now they had not been available together in a single combination inhaler due to technical challenges in developing them as a room-temperature stable formulation.

Flutiform had been developed as 3 doses, based on the doses of ICS and LABA in the other available ICS/LABA products and the relevant monotherapies. The labelled dose strengths of fluticasone in Flutiform were the same as those in Seretide Evohaler. Seretide Evohaler and Flutiform devices also delivered similar doses of fluticasone as shown below.

	Flutiform pMDI	Fluticasone Salmeterol pMDI
Low dose (mcg)		
Labelled	50/5	50/25
Delivered	46/4.5	44/21
Medium dose (mcg)		
Labelled	125/5	125/25
Delivered	115/4.5	110/21
High dose (mcg)		
Labelled	250/10	250/25
Delivered	230/9.0	220/21

Flutiform was developed in a pressurised metered dose inhaler (pMDI) device with a dose counter. pMDIs were commonly used inhaler devices in the UK and were very familiar to health professionals and patients. pMDIs all operated in a similar fashion and with similar instruction.

Dry powder inhalation (DPI) devices, differed significantly in their operation from pMDIs and also from each other. Napp was concerned that GlaxoSmithKline did not clearly differentiate between its pMDI (Seretide Evohaler) and DPI (Seretide Accuhaler) inhalers in this complaint, when describing study results, or in its promotional materials.

It was relevant and important to understand why Flutiform pMDI was positioned against Seretide Evohaler pMDI and not Seretide Accuhaler DPI. Correspondence received from GlaxoSmithKline highlighted the issue of device switching (ie pMDI or DPI) with respect to loss of control and increased consultation time, highlighting that this was a concern for a switch from Seretide pMDI to Flutiform pMDI. GlaxoSmithKline cited Thomas *et al* (2009) as the key source of evidence for this. However, Thomas *et al* did not present data on a switch between pMDI treatments; the authors instead reported on the issues of switching between different devices ie between pMDI, DPI and breath-actuated device where there was a significant difference in operation and therefore potential for misuse leading to loss of asthma control and consultation time to train on the new device.

In the complaint GlaxoSmithKline cited objections to several Committee for Medicinal products for Human Use (CHMP) regulatory guidelines cited by Napp. Disappointingly, several of these arguments were not raised with Napp during inter-company dialogue, but they had been addressed (see Point 1 below).

In 2010 Napp submitted an application for Flutiform to the CHMP of the European Medicines Agency (EMA) via the decentralised procedure, with the UK Medicines and Healthcare Products Regulatory Agency (MHRA) as the reference member state. This was for three ascending doses of 50mcg fluticasone/5mcg formoterol, 125mcg fluticasone/5mcg formoterol and 250mcg fluticasone/10mcg formoterol per actuation via a pMDI suspension. The application was reviewed initially by 22 EU member states and thereafter (as with other recent applications) by the CHMP.

Regarding the decentralised procedure, Napp noted that the Flutiform regulatory submission was a full clinical dossier with a large and comprehensive clinical package, not an abridged application The decentralised procedure started in June 2010. The indication sought was the regular treatment of asthma where the use of a combination product was appropriate: for patients not adequately controlled with inhaled corticosteroids and 'as required' inhaled short-acting β_2-agonist. ['Step-up' indication]. Or for patients already adequately controlled on both an inhaled corticosteroid and a long-acting β_2-agonist. ['Switch' indication].

The clinical development programme for Flutiform evaluated efficacy and safety in the intended patient population. Efficacy was demonstrated by measures of both lung function and clinical symptoms. The total clinical programme comprised 18 completed studies and included almost 5,000 patients. The five pivotal Flutiform Phase III studies included approximately 2,500 patients and the safety database included over 1,900 Flutiform-treated patients. Studies included both adolescents (12 to 18 years) and adults. Section 5.1 of the Flutiform SPC also described limited paediatric information in children 4-12 years, but as was clear in Section 4.4, Flutiform was not for use in children under 12 years of age until further data was available.

The five pivotal clinical studies were designed to compare the efficacy and safety of Flutiform with its individual components administered separately and with its individual components administered together but inhaled from separate inhalers. Supportive studies compared the efficacy and safety of Flutiform with other combination therapies including a study which compared Flutiform with Seretide Evohaler pMDI (Bodzenta-Lukaszyk *et al* 2011a). It was not 'dismissed' by the CHMP as stated by GlaxoSmithKline, but was always considered to be a supporting study as the necessary guidelines indicated that the pivotal studies should be against the components of the combination. The development programme also assessed the efficacy and safety of Flutiform administered either with or without a spacer device and investigated the efficacy and safety of Flutiform across relevant subgroups. The CHMP and MHRA were consulted and they supported the clinical study designs in the Phase III clinical development programme and the use of pre-dose FEV1 as the primary endpoint for efficacy in respect of corticosteroid effect. It was therefore clear that the relevant guidelines had been correctly followed.

As noted by GlaxoSmithKline, asthma control was one of two principal treatment goals in asthma management (the other being the reduction of exacerbation risk). It was a multidimensional concept incorporating symptoms, night-time awakenings, use of rescue medication, lung function and activity limitation.

Although pre-dose FEV1 was the main endpoint in the studies submitted, a number of other relevant patient symptom efficacy measures were captured as secondary endpoints. As such the application demonstrated that Flutiform provided improved asthma control compared with fluticasone monotherapy and a reduction in exacerbation risk. These data were reviewed and accepted by the EMA as evidence of the efficacy of Flutiform. The EMA also accepted extrapolation of an 8-12 weeks study duration to the longer term. The Flutiform European Public Assessment Report (EPAR) stated (page 9, paragraph 2):

'In conclusion, given the long-term predictive value of FEV1, given the static nature of FEV1 after 8 to 12 weeks of treatment, and given the pattern of the FEV1 data observed in the five pivotal studies, the CHMP considers there to be no reason to anticipate that the long-term exacerbation risk with Flutiform may exceed that with fluticasone propionate alone (the "Step-up" indication) or fluticasone propionate in combination with formoterol fumarate (the "Switch" indication). These conclusions based on an indirect assessment of future exacerbation risk are consistent with and support those based on a direct observation of exacerbation rates during the clinical studies.

The CHMP was of the view that clinical data generated over 6 to 12 months to further elucidate the level of asthma control and to further assess exacerbation rates seen with Flutiform compared with fluticasone propionate administered concomitantly with formoterol fumarate or administered alone, are not required.'

Furthermore, the EPAR (page 7, paragraph 6) noted:

'Turning to the available data in the Applicant's studies, for the "Step-up" comparison the odds of "any" exacerbation were 33% higher in fluticasone propionate- than Flutiform-treated patients (p = 0.019) whilst the annual exacerbation rate was 49% higher in fluticasone propionate- than Flutiform-treated patients (p = 0.004). These data were generated from the five pivotal 8- to 12-week studies and demonstrate the protective benefit of Flutiform against exacerbations compared with fluticasone propionate monotherapy. Published sources indicate that these treatment differences would at worst remain static and at best improve in favour of Flutiform over the longer-term.'

In conclusion, the CHMP had considered a large and comprehensive package of data and recommended Flutiform for the treatment of asthma where a combination product was appropriate:

'Having considered the overall submitted data provided by the Applicant in writing and during the oral explanation, the CHMP concluded that the benefit-risk balance of Flutiform 50/5, 125/5 & 250/10 micrograms pressurised inhalation, suspension is positive under normal conditions of use.

The CHMP considered all concerns raised by the objecting member state to be adequately addressed and that they should not prevent the authorization of the product.

Therefore, the CHMP recommended the granting of the marketing authorization for Flutiform 50/5, 125/5 & 250/10 micrograms pressurised inhalation, suspension.'

Whilst Flutiform was a new combination pMDI inhaler there was still a significant amount of clinical data to support its use. The package included five pivotal studies of 8-12 weeks' duration in both adults and adolescents; three supporting studies providing evidence including a paediatric study vs Seretide and two further supporting studies (one long-term and one vs monotherapies). Napp summarised the efficacy endpoints from the Phase III studies.

1 Claim 'Comparable clinical efficacy'

The claim 'Comparable clinical efficacy (p=0.007; open label)' appeared as the second bullet point beneath the subheading 'Prescribe flutiform instead of Seretide Evohaler because it can deliver:' on the second page of leavepiece 1.

Beneath a subheading 'An introduction to flutiform', leavepiece 2 stated 'Clinical trial data have shown that in patients with mild to moderate-severe persistent asthma: flutiform had comparable clinical efficacy to Seretide Evohaler (p=0.007; open label)'.

Both claims were referenced to Bodzenta-Lukaszyk *et al* (2011a).

COMPLAINT

GlaxoSmithKline explained that there were two published Flutiform studies; Bodzenta-Lukaszyk *et al* (2011a) (open label, randomised: Seretide Evohaler vs Flutiform) and Bodzenta-Lukaszyk *et al* (2011b) (double-blind, randomised: Flutiform vs fluticasone plus formoterol).

GlaxoSmithKline alleged that the claim 'Comparable clinical efficacy' (between Seretide and Flutiform) did not reflect the current available evidence, misled through exaggeration of the available data and was not sufficiently complete to enable the recipient to form their own opinion of the potential differences between the medicines.

Flutiform was a new combination inhaler that combined two medicines that had not been previously licensed for use in combination in an inhaler and were different from those seen in Seretide. This new combination of medicines and excipients was delivered to the lung using different technological processes to the Seretide Evohaler resulting in different pharmacokinetic and pharmacodynamic properties.

The only evidence presented by Napp to substantiate 'comparable clinical efficacy' was a 12 week, open label study which examined the low and medium doses of both products in adult (aged 18 years or more) asthma patients. This study demonstrated non-inferiority of a lung function parameter (FEV1) as a primary outcome and discontinuation due to lack of efficacy as a secondary outcome. While FEV1 was, unarguably, an important measure of lung function it needed to be combined with clinical outcomes in order to demonstrate accepted criteria of clinical efficacy. Discontinuation due to study medication was not, *per se*, a recognised clinical measure of control and in this regard GlaxoSmithKline referred to the summary of clinical symptoms provided above in its background comments.

GlaxoSmithKline submitted that the evidence presented by Napp did not demonstrate or substantiate a claim of comparable clinical efficacy because:

i The bioavailability of steroid component of Flutiform had not been studied but current evidence suggested that this was likely to be lower than that for Seretide so surrogate markers of clinical efficacy were inadequate.

Seretide and Flutiform had different pharmacokinetic properties. This meant that to establish clinical equivalence, equivalence of clinical and lung function endpoints were required in adolescent and adult patients over six months.

The relationship between the bioavailability of Seretide and Flutiform had not been studied so was unknown. Hochhaus and Kaiser suggested that Flutiform delivered 24-31% less fluticasone to the lungs than GlaxoSmithKline fluticasone monotherapy. When salmeterol and fluticasone propionate were administered in combination, as Seretide, by the inhaled route, the pharmacokinetics of each component were similar to those observed when the medicines were administered separately.

Because of the different pharmacokinetic properties, it was therefore essential when claiming these two products had a comparable clinical effect, that robust clinical evidence was available to support such key claims and comparisons. GlaxoSmithKline alleged that Napp had failed to demonstrate adequate evidence to justify the claims.

ii The clinical evidence presented to demonstrate comparable clinical efficacy was inadequate to substantiate this claim.

GlaxoSmithKline submitted that Napp used FEV1 alone to demonstrate clinical comparability between Seretide Evohaler and Flutiform. Given that the two products contained different medicines and had different steroid bioavailability, this exaggerated the current evidence.

The CPMP/EWP/2922/01 guidance on the clinical investigation of asthma medicines defined the two categories of endpoints as lung function and clinical evidence. The guideline advised that 'for a new controller treatment ... an equal emphasis should be placed on lung function and the symptom based clinical endpoints'. For controller medicines it was also advised that 'for moderate and severe persistent asthma, symptom based endpoints are particularly important. These may include the frequency of exacerbations and an assessment of asthma control'. The evidence referenced by Napp did not include severe asthmatics and did not demonstrate non-inferiority for Flutiform compared with Seretide for any of the accepted parameters of clinical control.

In inter-company dialogue, Napp had justified the selection of study endpoints by reference to the CPMP/EWP/4151/00 Rev.1 Guideline that provided requirements for clinical documentation related to the application for marketing authorization through the abridged route (ie was for the demonstration of therapeutic equivalence between two products that were essentially the same). GlaxoSmithKline believed that reference to this guideline was incorrect because:

- Flutiform did not meet the requirements for application for a marketing authorization through the abridged route when compared with Seretide
- Flutiform differed from Seretide in terms of active ingredients, excipients and delivery technology
- Lung deposition and pharmacokinetic differences between Seretide and Flutiform had not been studied. Current evidence suggested that steroid bioavailability was likely to be substantially lower for Flutiform when compared with Seretide
- The EPAR stated that the CHMP dismissed Bodzenta-Lukaszyk *et al* (2011a) as not being relevant to the application for marketing authorization.

In addition, if the CPMP/EWP/4151/00 Rev.1 Guideline was relevant, the Seretide/Flutiform head-to-head data differed significantly from the guideline recommendations. Thus, any conclusions based on reference to this guideline exaggerated the available evidence. The following examples demonstrated where the evidence presented by Napp deviated from the guideline recommendations for demonstrating therapeutic equivalence through an abridged marketing authorization application:

- A double-blind, double-dummy design was recommended
- 'For new fixed combination products with no approved fixed combination reference product the inclusion of an additional treatment arm in which patients would receive the ICS component alone is necessary' (Section 6.2.3.3)
- Adolescents required separate study (Section 9)
- The study would need to show a significant statistical dose response relationship (Section 6.2.3.3)
- Bronchial challenge response endpoints were recommended (Section 6.2.2.2, 6.2.3.1).

For the reasons stated, if regulatory guidance documents were referenced, GlaxoSmithKline believed that guidance document CPMP/EWP/2922/01 (Note for guidance on the clinical investigation of medicinal products in the treatment of asthma, November 2002) was the more suitable reference for the selection of the necessary study endpoints required to demonstrate clinical efficacy most appropriately.

The CPMP/EWP/2922/01 guidance on the clinical investigation of asthma medicines defined the two categories of endpoints as lung function and clinical evidence; the guideline advised that 'for a new controller treatment ... an equal emphasis should be placed on lung function and the symptom based clinical endpoints'. For controller medications it was also advised that 'for moderate and severe persistent asthma, symptom based endpoints are particularly important. These may include the frequency of exacerbations and an assessment of asthma control'. The evidence cited by Napp did not include severe asthmatics and did not demonstrate non-inferiority for Flutiform compared with Seretide for any of the accepted parameters of clinical control.

This guidance also advised that 'Claims for chronic treatment should be supported by the results from randomised, double-blind, parallel, controlled clinical trials of at least six months' duration' and 'equal emphasis should be placed on lung function and the symptom based clinical endpoint'. GlaxoSmithKline believed that this was especially relevant when comparability claims were based upon head-to-head data for two products that were different in many respects.

In inter-company dialogue Napp also referenced a ATS/ERS 2009 consensus statement to justify the extrapolation of FEV1 non-inferiority to infer clinical comparability. The consensus statement advised that FEV1 was one of the main spirometric parameters relevant to asthma. GlaxoSmithKline acknowledged that FEV1 was one of the fundamental lung function parameters and needed to be measured within a clinical trial and also in clinical practice. However, the consensus statement also advised:

'Symptoms and lung function represent different domains of asthma and they correlate poorly over time in individual patients, so both need to be monitored by clinicians assessing control in clinical practice.'

'Based on experience with anti-inflammatory therapy, it is often assumed that future risk of exacerbations will directly parallel changes in current clinical control. However these two aspects are not necessarily concordant ... with combination ICS/LABA.'

'Given that the goals of asthma treatment relate to both the achievement of good control and the minimization of future risk, it is not appropriate to specify a single primary endpoint for the assessment of asthma control. Studies of clinical efficacy and effectiveness should use appropriate endpoints which capture both aspects of asthma control.'

'Symptom scores in adults and children generally have moderate or weak correlations with other asthma outcomes, including static lung function, PEF variability, airway reactivity, and air inflammation,

consistent with the fact that these represent different domains of asthma control.'

'It is not appropriate to specify a single primary endpoint for the assessment of asthma control.'

'Many studies have reported low to moderate relationships between airflow limitation (measure by FEV1), respiratory symptoms and health related quality of life.'

It was therefore unfair and flawed to represent the limited evidence available and extrapolate FEV1 to conclude that Seretide and Flutiform were clinically comparable. The aim of combination inhaled therapies was to ensure good asthma control irrespective of the product prescribed. Where, as argued, the products were sufficiently different, claims of comparability based on the use of surrogate parameters which were short-term markers of lung function were clearly inadequate, inappropriate and ill advised. To do so was disparaging and sought to reduce confidence in the detailed evidence generated over time by the research-based pharmaceutical industry.

iii The patient selection was inadequate to allow extrapolation to all asthma severities and licensed age ranges.

As evidenced by the low exacerbation rates observed in the Seretide/Flutiform head-to-head study, severe patients were not included. In Bodzenta-Lukaszyk *et al* (2011a) exacerbation rates of 14% were seen over 12 weeks in patients taking Flutiform compared with 35.1% seen over 8 weeks in patients taking Flutiform in Bodzenta-Lukaszyk *et al* (2011b). In both studies, numerically more patients taking Flutiform experienced severe exacerbations than those patients taking Seretide or GlaxoSmithKline fluticasone propionate. The current head-to-head data were not of sufficient duration nor had sufficient power to determine whether this result might represent a discriminatory effect between the two products due to the differences in steroid bioavailability.

Adolescent patients had also not been included in the head-to-head study (Bodzenta-Lukaszyk *et al* (2011a)). Napp indicated that the selection of patients for demonstration of clinical comparability could be referenced to CPMP/EWP/4151/00 Rev.1. Although GlaxoSmithKline disputed Napp's use of this guideline to justify its promotional approach, it did nevertheless advise that adolescents should be included in asthma clinical studies.

In contrast, the clinical efficacy of Seretide in adolescents and adults had been proven in the GOAL study which demonstrated that the majority of patients (62-75%) previously symptomatic on ICS were able to achieve guideline-defined control with the regular use of Seretide. Guideline defined control was defined by achieving two or more of the following criteria:

- Rescue salbutamol use ≤2 days and ≤4 occasions per week
- Symptoms score >1 on ≤2 days per week
- ≥80% predicted morning PEF every day.

and all of the following criteria:

- No night-time wakening due to asthma
- No exacerbations
- No emergency visits
- No treatment-related adverse effects enforcing a change in asthma therapy.

The GOAL study was one of the pivotal studies in respiratory medicine and defined the standard of care for asthma patients. The claim that Flutiform and Seretide had comparable clinical efficacy implied that the above outcomes would be achieved with Flutiform. The current evidence did not substantiate that claim.

iv The doses studied could not be extrapolated to infer clinical comparability of all doses.

Only the mid and low doses of Seretide Evohaler and Flutiform had been compared. In inter-company dialogue Napp maintained that these results could be extrapolated to indicate comparability of high doses. Napp justified the appropriateness of comparing the high dose strength and stated that in vitro dose linearity had been proven as part of the marketing authorization, and referred to CPMP/EWP/4151/00 Rev.1 Guidelines and stated:

'If dose linearity is demonstrated in vitro when different dose strengths of a known active substance are sought it may be sufficient to establish therapeutic equivalence clinically with only one strength of the active substance. It is usually appropriate to study the lowest strength, at more than one dose level, to enhance the sensitivity of the study.'

GlaxoSmithKline was not aware that dose linearity of Flutiform compared with Seretide had been studied, however, as previously discussed; CPMP/EWP/4151/00 Rev.1 specifically provided guidance for establishing equivalence between two products that were essentially the same. These guidelines were therefore not relevant as Flutiform was not a generic version of Seretide and the relative bioavailability of fluticasone was likely to be substantially lower in Flutiform. In addition, the Flutiform head-to-head study was powered to detect non-inferiority of the primary endpoint of FEV1, not equivalence.

Given the likely low bioavailability of Flutiform when compared with Seretide, comparing the lower strengths of two products in milder patients less likely to exacerbate meant that extrapolating the results and concluding that all patients would achieve the same efficacy response was not scientifically robust.

In summary, it was flawed to represent the limited evidence available and extrapolate FEV1 to conclude clinical comparability between Seretide and Flutiform. The aim of combination inhaled therapies was to ensure good asthma control irrespective of the product prescribed. Where, as argued, the products were sufficiently different, claims of comparability based on the use of surrogate parameters which were short-term markers of lung function were clearly inadequate, inappropriate and ill advised. To do so was disparaging and reduced confidence in the detailed evidence generated over time by the research-based pharmaceutical industry.

GlaxoSmithKline alleged that exaggerating the current available evidence to suggest that Flutiform and Seretide had clinically comparable efficacy breached Clauses 7.2, 7.3, and 7.4.

RESPONSE

Napp referred to data which it had provided to summarise the efficacy endpoints used in various studies. GlaxoSmithKline incorrectly stated that 'this [Flutiform vs Seretide] study demonstrated non inferiority of a lung function parameter (FEV1) as a primary outcome and discontinuation due to lack of efficacy as a secondary outcome'. GlaxoSmithKline failed to acknowledge that there were multiple secondary outcomes, including both lung function and patient outcomes.

Napp responded to the four arguments proposed by GlaxoSmithKline as to why the claim 'comparable clinical efficacy (P = 0.007; open label)' did not comply with the Code.

i The bioavailability of the steroid component of Flutiform had not been studied but current evidence suggested that this was likely to be lower than that for Seretide so surrogate markers of clinical efficacy were inadequate.

Napp stated that these data had not been raised by GlaxoSmithKline during inter-company dialogue. However, the bioavailability of Flutiform was discussed during the decentralised procedure regulatory submission and the conclusions of the CHMP and MHRA were publicly available in the EPAR. GlaxoSmithKline was therefore aware of the discussions and conclusions of the CHMP and the MHRA.

It was clear from the literature that pharmacokinetic data did not correlate accurately with the clinical outcomes. This position was supported by the CHMP and the MHRA. The EPAR stated that:

'Literature data indicate that even if the PK [pharmacokinetic] data accurately reflect comparative pulmonary drug deposition for Flutiform versus GSK fluticasone propionate pMDI, such differences are not of clinical relevance. Furthermore, the discordance between the PK and PD [pharmacodynamic] data for Flutiform suggests that the PK data do not accurately reflect comparative pulmonary deposition and are not a valid surrogate for clinical effect.'

The CHMP noted that the magnitude of the difference presented in the abstract by Hochhaus and Kaiser was within the normal bounds of variability for inhaled medicines.

'The CHMP noted that the differences of the magnitude observed between Flutiform and GSK fluticasone propionate in Study FLT1501 (67% relative bioavailability) are within the same range of variance as observed within patients (from inhalation to inhalation), between different batches of the same product and between different inhalers containing the same or more than one of the same active.'

In summary, the CHMP and MHRA clearly considered that the pharmacokinetic data did not reflect clinical efficacy nor provide an accurate reflection of lung deposition.

Furthermore GlaxoSmithKline fluticasone pharmacokinetic data in the UK Seretide Evohaler SPC (Section 5.2) indicated that absolute bioavailability varied between 5-11% of the nominal dose depending on the inhalation device used. These data indicated one device delivered less than half the fluticasone than another device, again supporting significant variability. Napp noted that although GlaxoSmithKline (nor the UK SPC) did not note the devices behind these figures, the data were available in the New Zealand Data Sheet for Seretide inhaler (Aerosol device). This document reported that the fluticasone propionate bioavailability for Seretide Inhaler (Aerosol) was 5.3% compared with 10.9% for fluticasone propionate monotherapy in the same device, which would suggest 51% less fluticasone delivery from Seretide than the monotherapy – more than the difference reported by Hochhaus and Kaiser (24-31%).

'The absolute bioavailability of fluticasone propionate for each of the available inhaler devices has been estimated from within and between study comparisons of inhaled and intravenous pharmacokinetic data. In healthy adult subjects the absolute bioavailability has been estimated for fluticasone propionate Accuhaler (7.8%), fluticasone propionate Inhaler (10.9%), Seretide Inhaler (5.3%) and Seretide Accuhaler (5.5%) respectively.' (New Zealand Data Sheet).

In conclusion, as the CHMP and MHRA noted that the difference seen was clearly within normal bounds of variability and comparable to that between Seretide and the fluticasone monotherapy suggested in the New Zealand Data Sheet, the assertion that differences in bioavailability made Napp's claim of clinical efficacy inadequate were unfounded and did not support a breach of Clauses 7.2, 7.3 or 7.4.

ii The clinical evidence presented to demonstrate comparable clinical efficacy was inadequate to substantiate this claim.

Napp did not use FEV1 alone to demonstrate clinical comparability between Seretide Evohaler and Flutiform.

As outlined above, the body of clinical evidence demonstrated that Flutiform was efficacious both in terms of lung function and patient clinical symptom domains. The findings were entirely in keeping with the expected outcome from these two widely known and well studied medicines.

Additionally the clinical data presented in the leavepieces regarding the direct head-to-head study of Flutiform pMDI vs Seretide Evohaler pMDI (Bodzenta-Lukaszyk *et al* 2011a) successfully demonstrated statistical non-inferiority for the primary endpoint of FEV1. The authors concluded that: 'Analysis of additional efficacy parameters such as other lung function tests,

patient-reported outcomes, rescue medication use, asthma exacerbations and [asthma quality of life questionnaire] AQLQ scores yielded comparable results for the two treatment groups'. This was not a study to demonstrate clinical equivalence.

The claim in question was comparable clinical efficacy and in this regard Napp referred to Case AUTH/2515/6/12, Allergan/Director v Merz in which the Panel's ruling of no breach of the Code was upheld by the Appeal Board.

'In the Appeal Board's view 'Comparable efficacy' did not imply equivalence.'

Napp also referred to Case AUTH/2357/9/10, GP v Boehringer Ingelheim:

'The Panel did not consider that comparability implied equivalence – comparable only meant that the two products were able to be compared.'

Building on the principles set out in these cases, Napp submitted that given the results of the Flutiform vs Seretide study, and given the results of the clinical package as a whole which supported these results, a claim of comparability was accurate. This evidence was acceptable to grant a marketing authorization with the therapeutic indication of:

'This fixed-dose combination of fluticasone propionate and formoterol fumarate (Flutiform inhaler) is indicated in the regular treatment of asthma where the use of a combination product (an inhaled corticosteroid and a long-acting ß$_2$-agonist) is appropriate:

For patients not adequately controlled with inhaled corticosteroids and 'as required' inhaled short-acting ß$_2$-agonist.

or

For patients already adequately controlled on both an inhaled corticosteroid and a long-acting ß$_2$-agonist.'

This was very similar to the therapeutic indication for Seretide Evohaler:

'Seretide is indicated in the regular treatment of asthma where use of a combination product (long-acting ß$_2$-agonist and inhaled corticosteroid) is appropriate:

Patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short-acting ß$_2$-agonist

or

Patients already adequately controlled on both inhaled corticosteroid and long-acting ß$_2$-agonist.'

Napp noted that the use in patients already controlled on any corticosteroid or long-acting ß$_2$-agonist was permitted. Clearly Flutiform had virtually the same indication as Seretide Evohaler and had an indication which would allow Flutiform to be used in patients already adequately controlled on Seretide Evohaler.

FEV1 was a well established and accepted measure for comparing the efficacy of inhaled asthma medicines (Reddel *et al* 2009). The decision to use FEV1 as a primary endpoint was based on principles adopted from a number of CHMP guidelines as already discussed, including those referenced by Napp during inter-company dialogue, and those referenced by GlaxoSmithKline. The aim of this research was to demonstrate that Flutiform was clinically efficacious. To this end a package of clinical studies, predominantly 8-12 week studies which used FEV1 as the primary endpoint, was developed. Secondary endpoints were not powered to demonstrate non-inferiority to Seretide and yet yielded similar results between Seretide Evohaler and Flutiform. The decision that Flutiform was clinically efficacious, and the subsequent granting of the marketing authorization for Flutiform by the EMA, was based largely on studies using FEV1 as the primary endpoint.

GlaxoSmithKline alleged that the duration of the studies presented did not substantiate a claim due to no assessment of future risk as highlighted by the consensus statement by the ATS and the ERS. The predictive nature of 8-12 week FEV1 studies was extensively discussed during the regulatory process. The body of evidence for both primary and secondary endpoints generated for Flutiform, including the comparator study with Seretide, clearly demonstrated that there were clinically comparable outcomes across a range of domains. The CHMP and MHRA stated:

'In conclusion, given the long-term predictive value of FEV1, given the static nature of FEV1 after 8 to 12 weeks of treatment, and given the pattern of the FEV1 data observed in the five pivotal studies, the CHMP considers there to be no reason to anticipate that the long-term exacerbation risk with Flutiform may exceed that with fluticasone propionate alone (the "Step-up" indication) or fluticasone propionate in combination with formoterol fumarate (the "Switch" indication). These conclusions based on an indirect assessment of future exacerbation risk are consistent with and support those based on a direct observation of exacerbation rates during the clinical studies.

The CHMP was of the view that clinical data generated over 6 to 12 months to further elucidate the level of asthma control and to further assess exacerbation rates seen with Flutiform compared with fluticasone propionate administered concomitantly with formoterol fumarate or administered alone, are not required.'

Furthermore, all clinical secondary endpoints were consistent with the primary endpoint and showed comparable efficacy between Flutiform and Seretide Evohaler:

- Discontinuation due to lack of efficacy
- Change from baseline to week 12 in pre-dose FEV1
- Rescue medication use

- Mean PEF
- Asthma symptom score and sleep disturbance scores
- Asthma quality of life questionnaire scores
- Number of adverse events
- Number of exacerbations.

Both Flutiform and Seretide Evohaler were efficacious products and this formed the basis of Napp's claim. Both products had a body of data to support this. When compared in a direct head-to-head study Flutiform was found to be non-inferior, in a well recognised and accepted clinical end point. Napp submitted that this finding was supported by the secondary endpoints in the study.

Importantly these findings were supportive and in line with the other regulatory studies proving the efficacy of Flutiform. GlaxoSmithKline inferred that for products to be considered to be clinically comparable they must have the same supporting data. The claim of comparable clinical efficacy did not claim or imply clinical equivalence and was adequately supported by the available evidence. Napp stated that in view of the CHMP's conclusions and the use of appropriate end points in the Flutiform studies, 'comparable efficacy' was an entirely appropriate claim.

iii The patient selection was inadequate to allow extrapolation to all asthma severities and licensed age ranges

Studies were conducted in a sample of a population and these results were then extrapolated to the treatment population: this was a key principle of why studies were carried out. This principle was justified in this claim due to the wide body of evidence for Flutiform over a range of asthma severities and ages.

These studies included adolescents and also severe patients. The conclusion of these studies was that there was sufficient evidence to grant a 'switch licence':

'With regard to the "Switch" therapy, the CHMP accepted the discussions presented by the Applicant and was of the view that the clinical effects of Flutiform in respect of asthma control and exacerbation risk are comparable with/similar to the clinical effects of GSK fluticasone propionate and Novartis formoterol fumarate given concomitantly.

The magnitude of changes seen on a range of secondary endpoints helps to quantify the clinical relevance of the effects seen on pulmonary function and on exacerbation rate. Across a broad range of endpoints such as discontinuation due to lack of efficacy, symptom-free days and nights and the amount of rescue medication, the size of effect seen is clinically important. These findings should be taken together with the results that show that the clinical effects of Flutiform are comparable with the clinical effects of GSK fluticasone propionate and Novartis formoterol fumarate given concomitantly. This provides further support for the clinical relevance of the effects seen with Flutiform.' (EPAR section 2.2, page 8, paragraphs 2 and 3)

The Flutiform vs Seretide study was carried out in a population of mild to moderate-severe asthma patients over the age of 18, and concluded non-inferiority between the two products. The results of other studies with different age ranges (including 12 years and over) and severities (including severe), gave similar results as expected from two widely used and investigated molecules.

Specifically GlaxoSmithKline alleged that severe patients were excluded from the Seretide/ Flutiform head-to-head study. The patient selection criteria for this study included patients with a FEV1 predicted between 40-85% of normal values. Whilst Napp acknowledged that asthma severity could be determined in a number of ways, it submitted that this study included patients with severe asthma. The range of FEV1 was from 41-85% consistent with a range of asthma severity including the severe end of the spectrum. 77% of patients in this study were on an ICS/LABA so patients could be severe but well controlled on an ICS/LABA and therefore have low exacerbation risk as found in the results.

Data from these further studies did not indicate that it was invalid to extrapolate the comparability seen in clinical efficacy between Flutiform and Seretide as seen in the head-to-head study to the severe or adolescent patient groups.

Furthermore, GlaxoSmithKline alleged that the claim of comparable clinical efficacy ($p = 0.007$; open label) was unacceptable because Napp had not replicated the evidence supporting Seretide Accuhaler in the GOAL study. Napp acknowledged the robustness of the GOAL study. The GOAL study was a pivotal study that confirmed that ICS/LABA therapy provided greater asthma control than ICS monotherapy alone on both asthma control and exacerbation risk. This changed treatment practice and established ICS/LABA therapy as one of the cornerstones of asthma treatment. Napp submitted that it did not need to repeat the GOAL study for Flutiform. It had already highlighted, however, that the device used in the GOAL study was the Seretide Accuhaler, a dry powder inhaler device (DPI) and not a pMDI (see introductory section) such as Seretide Evohaler or indeed Flutiform. The GOAL study provided evidence for asthma maintenance therapy in adolescents (over age 12) but not for the entire licensed indication of Seretide, as the licence included the age 4 years and above.

However, at no stage did the leavepiece claim reference control, guideline defined control or the GOAL study.

In conclusion, Napp refuted the allegation that the patient selection was inadequate to allow extrapolation to all asthma severities and licensed age ranges. Napp maintained that severe asthmatic patients were included in both the Seretide vs Flutiform head-to-head study and in other studies of the clinical development programme leading to registration. Adolescents had also been studied, as well as limited data generated in children 4-12 years.

iv The doses studied cannot be extrapolated to infer clinical comparability of all doses

Napp referred to its response in inter-company dialogue. The following guidelines on the principle of extrapolation came from the most current CHMP guidelines (Section 4.5 CPMP/EWP/4151/00 Rev.1) on the development of orally inhaled products (OIP):

'Dose linearity should be investigated in vitro for both the test and the reference product across all proposed strengths.

If dose linearity is demonstrated in vitro when different dose strengths of a known active substance are sought it may be sufficient to establish therapeutic equivalence clinically with only one strength of the active substance. It is usually appropriate to study the lowest strength, at more than one dose level, to enhance the sensitivity of the study.'

The in vitro linearity of the fluticasone component of Flutiform across all doses had been demonstrated and was accepted as part of the marketing authorization application. Linearity of the fluticasone component of Flutiform had been established and as with the Seretide SPC, 'there is a linear increase in systemic exposure of fluticasone with increasing inhaled dose' (SPC). It was therefore reasonable to infer that similar relative fluticasone bioavailability would be observed for the comparison of all strengths of Flutiform vs the corresponding strengths of Seretide.

Pharmacokinetic linearity had been demonstrated for inhaled formoterol over a (delivered) dose range of 4.5g to 36g (Derom *et al* 2007). The in vitro linearity of the formoterol component of Flutiform across dose strengths had also been demonstrated and was accepted as part of the marketing authorization application. Although to date, no study had compared the efficacy of Flutiform and Seretide Evohaler at their highest licensed doses, given the similar efficacy and tolerability profiles at the low and medium doses, and the dose linearity of the components of Flutiform, it might reasonably be inferred that, at their highest doses, both products would be likely to have comparable efficacy and safety profiles.

Furthermore the efficacy of the high dose was clearly demonstrated in the published pivotal regulatory study (FLT 3503; Bodzenta-Lukaszyk *et al* (2011b)). This study compared high strength Flutiform with high strength fluticasone monotherapy (GlaxoSmithKline fluticasone pMDI) when given concurrently with formoterol (Novartis formoterol pMDI). Considering formoterol and salmeterol had similar bronchodilatory effects over 12 hours (although as previously noted formoterol had a significantly faster onset), comparable efficacy for the high dose treatments of Seretide and Flutiform could clearly be expected. This study also confirmed superiority of Flutiform over GlaxoSmithKline fluticasone monotherapy high dose on several clinical endpoints including asthma symptom score, symptom free days, awakening-free nights, and AQLQ.

In summary, Napp maintained that Flutiform and Seretide Evohaler were clinically comparable, and it did not claim to have demonstrated clinical equivalence. Napp had presented extensive and not limited evidence for this from the total clinical development dossier, including the head-to-head study. Napp had conducted studies of appropriate duration, including moderate and severe asthma patients and adolescents, and had fully justified the use of two dose strengths. It strongly refuted the claim that its studies were 'clearly inadequate, inappropriate and ill advised', especially when the clinical development programme which led to a successful European registration was conceived in collaboration with the MHRA and accepted by the EMA.

For the reasons stated above Napp submitted that it had not exaggerated the current available evidence to claim clinical comparability between Flutiform and Seretide Evohaler and did not agree that it had breached Clauses 7.2, 7.3 and 7.4.

PANEL RULING

The Panel noted that the claim at issue 'Comparable clinical efficacy' was referenced to Bodzenta-Lukaszyk *et al* (2011a), a 12 week, open-label, randomised study designed to demonstrate the non-inferiority of Flutiform vs Seretide (100/500mcg or 250/50mcg twice daily) in controlling mild to moderate-severe persistent asthma in adult patients aged 18 years or over. No patients received the maximum dose of Flutiform (500/20mcg twice daily) or of Seretide (500/50mcg twice daily). The primary endpoint was non-inferiority based on mean FEV1. The secondary comparative endpoints included discontinuations due to lack of efficacy, time to onset of action, peak expiratory flow rates and other lung function parameters, amount of rescue medication use, asthma symptom scores, sleep disturbance due to asthma, daily corticosteroid doses and asthma exacerbations. The authors stated that the study demonstrated that Flutiform was comparable (non-inferior) to Seretide in terms of the primary endpoint (mean pre-dose FEV1 at week 12) and certain secondary efficacy endpoints in relation to FEV1 measurements and discontinuation due to lack of efficacy. Flutiform was superior to Seretide in terms of time to onset of action. The authors stated that analysis of additional efficacy parameters yielded 'similar results' (lung function tests, patient reported outcomes, rescue medication use, asthma exacerbations and AQLQ scores).

Whilst noting that FEV1 was a fundamental efficacy measurement, the Panel considered the broad unqualified claim 'comparable efficacy' implied more than a measurement of FEV1. In this regard the Panel noted that the secondary outcome data in Bodzenta-Lukaszyk *et al* (2011a) showed that Flutiform and Seretide were similar in a number of additional relevant efficacy measurements.

The Panel noted GlaxoSmithKline's submission that as evidenced by the low exacerbation rates, severe asthmatics were not included. The Panel also noted Napp's contrary comments and its submission that as 77% of patients were on a combination product severe asthmatics could be well-controlled and thus have

a low exacerbation risk. This was inconsistent with Napp's subsequent assertion that there was no further data to indicate that it was invalid to extrapolate the results of Bodzenta-Lukaszyk *et al* (2011a) to severe or adolescent asthmatics. Bodzenta-Lukaszyk *et al* (2011a) described the patient population as 'mild-to-moderate - severe, persistent asthmatics' which the Panel considered might be read as including patients who had asthma which was anything from mild- to moderately-severe. To be included in the study patients were required to demonstrate an FEV1 of ≥40% and ≤85% of predicted normal values. The Panel noted that Mansur and Kaiser (2012) defined eligible patients with mild-to- moderate - severe asthma as those with an FEV1 of between 40-85% of predicted normal values. The Panel also noted that the ATS/ ERS 2009 joint statement stated that asthma severity was defined as the difficulty of controlling asthma with treatment. Severity largely reflected the required level of treatment and the underlying disease state during treatment.

The Panel noted that Section 4.2 of the Flutiform SPC stated 'Flutiform inhaler in any strength is not recommended for use in children less than 12 years of age; Flutiform inhaler should not be used in this young age group'. In addition, it was stated that Flutiform 250/10mcg inhaler 'should not be used in adolescents'. The Panel noted that according to its SPC, Seretide 25/50mcg could be prescribed from the age of 4 years. There was no data available for use of Seretide in children aged under 4 years. From the age of 12 years children could be treated with all three doses of Seretide (25/50mcg, 25/125mcg and 25/250mcg).

The Panel noted that the heading to the page at issue in leavepiece 1 read 'Why should I prescribe Flutiform instead of Seretide Evohaler?' The subheading read 'Prescribe flutiform instead of Seretide Evohaler because it can deliver:'. The facing page detailed the high, medium and low doses of Flutiform. The Panel considered that many readers would already be familiar with the Seretide Evohaler which the Panel noted was first granted a market authorization in 2000. The Panel considered that the broad, unqualified claim 'Comparable clinical efficacy (P = 0.007, open label)' implied that Flutiform could be used in all of those patients for whom Seretide might be prescribed and that there was robust comparative clinical data in relation to all doses and patient populations and that was not so. The Panel noted that there was some comparative efficacy data but considered that insufficient information about the study had been provided to enable the reader to accurately interpret the claim which was consequently misleading and incapable of substantiation. The Panel noted that the first page of the detail aid stated that Flutiform was '[fluticasone/formoterol] combined for the first time for asthma maintenance therapy for patients 12 years and older (low and medium strengths); adults (all strengths)'. However, this statement was in a small font size such that, in the Panel's view, it would be missed by many readers. The Panel did not consider that the statement was prominent enough to set the rest of the leavepiece in context. In the Panel's view the statement on the first page did not negate the otherwise misleading impression given by the claim on page 2 of 'Comparable clinical efficacy'. A breach of Clauses 7.2, 7.3, and 7.4 was ruled.

The Panel noted that leavepiece 2 was different. A preceding bullet point explained that Flutiform 50/5mcg and 125/5mcg were licensed for use in patients aged 12 years and above. The immediate subheading to the claim in question made it clear that patients had mild to moderate-severe persistent asthma. However, it had not been made clear that only medium and low doses of Seretide Evohaler had been compared in patients aged 18 years or over. The Panel also noted its comments above about the secondary clinical endpoints in Bodzenta-Lukaszyk *et al* (2011a). On balance, the Panel considered that the rulings made in relation to leavepiece 1 also applied to leavepiece 2. The claim 'Flutiform had comparable clinical efficacy to Seretide Evohaler (P= 0.007; open label)' was not sufficiently qualified and was therefore misleading and incapable of substantiation; a breach of Clauses 7.2, 7.3 and 7.4 was ruled.

2 Claim 'The efficacy and tolerability of flutiform were sustained for up to 12 months'

The claim at issue appeared in leavepiece 2 directly beneath the claim at issue at Point 1 above 'Clinical trial data have shown that in patients with mild to moderate-severe persistent asthma: flutiform had comparable clinical efficacy to Seretide Evohaler (P = 0.007; open label)'.

The claim was referenced to Mansur (2008).

COMPLAINT

GlaxoSmithKline stated that Mansur (2008) was a 12 month, open label, safety study, with no comparator arm. The abstract was recently published as a full paper (Mansur and Kaiser 2012) wherein the full dataset was disclosed.

The publication did not support the claim 'The efficacy and tolerability of flutiform were sustained for up to 12 months'. GlaxoSmithKline alleged that the claim exaggerated the results as the study was a 12 month, open label, safety study, with no comparator arm. Also, the claim did not provide the reader with enough information to make an accurate assessment of the current evidence.

Mansur and Kaiser measured FEV1 as a secondary endpoint in a 12 month safety study utilising no comparator arm over the 12 months. The term 'efficacy' was broad, and did not relate to the actual evidence which only demonstrated spirometric secondary endpoints and did not demonstrate any clinical efficacy endpoints.

The claim 'The tolerability and efficacy of flutiform were sustained for up to 12 months' also appeared directly below the claim '… comparable clinical efficacy to Seretide Evohaler …'. GlaxoSmithKline alleged that the juxtaposition of these two claims misled the reader into believing 'comparable clinical efficacy' had been demonstrated over 12 months.

During inter-company dialogue Napp proposed a revision to read: 'The tolerability and efficacy of Flutiform were sustained for up to 12 months (open label spirometric secondary endpoints p<0.001)'.

GlaxoSmithKline acknowledged that the two claims referred to different references; however, it was not clear that the claims related to two separate studies. Readers might assume that the second study was an extension of the first.

GlaxoSmithKline noted that Napp disagreed with its request that in addition to the revision proposed above, Napp also include the phrase 'no comparator' within the body of the text. In GlaxoSmithKline's view this would ensure that when the two claims were juxtaposed, it would be clear to the reader that the two trials were indeed different and that this was not an extension of the head-to-head study. Napp declined and stated that the provision of a reference was adequate. GlaxoSmithKline did not agree that the provision of different references was justification for not making the facts clear to the reader.

GlaxoSmithKline alleged that the juxtaposition of the two claims in both the current and proposed revised wording was misleading in breach of Clause 7.3.

RESPONSE

Napp submitted that the two parts of the claim (ie efficacy and tolerability), were substantiated, firstly by the Mansur abstract, 'Longterm safety study of FlutiForm HFA in asthma', and secondly by the full paper by Mansur and Kaiser, 'Long-term Safety and Efficacy of Fluticasone/Formoterol Combination Therapy in Asthma'. In the full paper, the efficacy variables, measured as secondary endpoints, were defined as spirometric measures with qualification of efficacy defined as significant improvements in measures of change, which included FEV1 and change in peak expiratory flow rate (PEFR) (l/min), specifically of:

a) mean change from pre-dose at baseline to pre-dose assessments at each visit and last visit, and
b) mean change from pre-dose at baseline to 1 hour post-dose at weeks 2 and 4 and at months 2 and 3.

Other measures of efficacy included FEV1 % predicted, forced vital capacity (FVC), asthma symptom scores and sleep disturbance scores.

Mansur and Kaiser demonstrated that the mean change at each patient visit was highly significant for all the spirometric efficacy parameters that were measured, and of particular note, the mean change in FEV1 and change in PEFR (l/min). These included the patient visits at months 3, 6 and 12.

Napp submitted that Mansur and Kaiser clearly defined the measures of efficacy, that they disclosed the full data set, the claim, 'The efficacy and tolerability of flutiform were sustained for up to 12 months', was substantiated and therefore provided the reader with enough information and guidance to make an accurate and balanced assessment of current, and other available evidence.

With regard to tolerability Napp submitted that Mansur and Kaiser, a 6-12 month open label safety study with patients aged 12 years and older, which included 466 patients in the full analysis set and 390 in the per protocol set, demonstrated that the incidence of adverse events, and also adverse event profile, [174 patients (36.9%), with the majority of adverse events either mild or moderate in severity] was in line and not unusual with that observed in previous long-term (1 year) studies of ICS/LABA combinations. For example, by comparison, after 1 year's treatment in adults with persistent asthma, the overall incidence of adverse events with fluticasone propionate/salmeterol xinafoate (250/50mcg twice daily) and budesonide/formoterol fumarate (200/6µg once daily or 200/6 - 400/12µg twice daily) was 48.6% and 52.3% respectively. Thus, the rates of adverse events reported by Mansur and Kaiser (36.9%) did not appear to be unusual for combination therapy administered for up to 1 year.

Mansur and Kaiser also reported that there were no significant or abnormal trends in clinical assessments and vital signs demonstrated over the 6-12 month period, that no deaths were reported, and that the 12 serious adverse events experienced by the 10 (2.12%) patients were considered not to be related or unlikely to be related to the study medicine. Therefore, Napp submitted that the claim at issue was substantiated.

Napp noted GlaxoSmithKline's allegation that the juxtaposition of the claim, placed below a separate claim of 'flutiform had comparable clinical efficacy to Seretide Evohaler (P = 0.007; open label)' misled readers as they would assume that this second study was an extension or subset of the first which it was clearly not. Napp submitted that it was clear that the two claims were placed under a title of 'Clinical trial data ...' which was meant in the plural and referred to separate independent data sets. Furthermore, the two independent claims were clearly and individually referenced and placed on separate lines; this reinforced their mutually exclusivity and independence. If Mansur and Kaiser had been derived from the same efficacy trial data as for the head-to head Seretide/Flutiform study it would be usual to indicate this with the same numbered reference. Lastly, there was no paragraph or sentence indentation of the second claim, which further supported the mutually exclusive individuality of these two claims – the second claim was clearly shown not to be part of a 'follow-on study' from the first.

In inter-company dialogue, GlaxoSmithKline disagreed that the provision of different references provided in small italics were justification for not making this clearer to the reader. In response Napp had noted that 'The different references are not in small italic on the leavepiece. They are superscript, are based on Vancouver style (www.icmje.org) and are at least 2mm in height (exceeding Clause 4.1 supplementary information for legibility – where a lower case letter 'x' is no less than 1 mm in height). Napp maintain that having two different reference numbers clearly do not imply that the two statements are from the same study.'

After inter-company dialogue, for the purposes of constructive progress and pragmatic resolution, Napp proposed to reword the claim for further clarification to: 'The tolerability and efficacy of flutiform were sustained for up to 12 months (open label spirometric secondary endpoints P<0.001)'. GlaxoSmithKline did

not accept this, and asked for additional wording to the claim that 'In a separate study the tolerability of ...'. Napp did not accept this for the reasons stated.

In conclusion, Napp submitted that the juxtaposition of the two claims in the leavepiece at issue followed the well accepted medical/scientific writing principles by being clearly independently and sequentially referenced. They were not misleading and not in breach of Clause 7.3.

PANEL RULING

The Panel noted GlaxoSmithKline had raised a number of allegations about the claim in question. During inter-company dialogue Napp had agreed to amend the claim. It appeared that the remaining unresolved issue was the allegation that a misleading impression was given by the juxtaposing of the claim in question to that considered at Point 1 above. This was the sole issue considered by the Panel.

The Panel noted that Mansur and Kaiser was an open label study in which mild to moderate-severe asthmatics age 12 years and over were treated twice daily with low or medium dose Flutiform for 6 months (n=256) or 12 months (n=216). The primary and secondary objectives were the long-term safety and efficacy of Flutiform. The study demonstrated statistically significant improvements overall and for both treatment groups for each efficacy assessment. Flutiform demonstrated a good safety and efficacy profile over the 12 month study period.

The Panel noted that the claim at issue 'The efficacy and tolerability of Flutiform were sustained for up to 12 months' appeared immediately beneath that at issue at Point 1 above, 'Flutiform had comparable clinical efficacy to Seretide Evohaler (P= 0.007, open label)'. The Panel considered that the juxtaposing of the claims was such that the claim at issue would inevitably be read in light of that preceding it and thus readers would infer that comparable clinical efficacy with Seretide Evohaler was demonstrated for up to 12 months and that was not so. The claim in question was misleading on this point as alleged and a breach of Clause 7.3 was ruled.

3 Question 'Why should I prescribe flutiform instead of Seretide Evohaler?'

This question appeared in leavepiece 1 as the heading to page 2; it was presented as a search in a web browser. The question was followed by 'Prescribe flutiform instead of Seretide Evohaler because it can deliver:' which was followed by four bullet points.

COMPLAINT

GlaxoSmithKline alleged that Flutiform was presented as a direct substitute to Seretide Evohaler but it was not a suitable substitute for all patients who were eligible for Seretide. There were several clinically important differences that were not mentioned in the leavepiece. The only difference between the two products highlighted in the leavepiece was that Flutiform had a faster onset of action, although no clinical rationale was provided to support why, in maintenance therapy, a faster onset of action was relevant. The claim for a faster onset of action claim was addressed in Point 5 below.

Seretide Evohaler and Flutiform differed in three important and clinically relevant aspects. Firstly, Seretide 50 Evohaler was licensed from 4 years and older whilst Seretide 125 and 250 Evohalers were licensed from age 12 years and older. Flutiform 50 and 125 were licensed from 12 years and older and Flutiform 250 was licensed from age 18 years and older. Secondly, unlike Seretide, Flutiform contained ethanol and so it was an unsuitable treatment for certain ethnic groups and thirdly, Flutiform was licensed for use with the AeroChamber Plus spacer device only. Seretide was licensed for use with both the Volumatic and AeroChamber Plus spacer devices.

GlaxoSmithKline alleged that the omission of clinically important marketing authorization differences when advising that Flutiform was an alternative treatment option to Seretide Evohaler misled prescribers. The information presented was not fair, balanced or objective and created confusion between the two products. As presented, it was selective and insufficiently complete and so the recipient could not determine an accurate or comprehensive view of the therapeutic relevance and value of the medicine. The omission of key information detailing the licensed differences meant that prescribers were not informed that Flutiform was unsuitable for some patients prescribed Seretide. GlaxoSmithKline alleged that this approach might encourage off-label prescribing and usage that compromised safety and put patients at risk in breach of Clauses 7.2, 7.3 and 7.4.

RESPONSE

Napp submitted that the full licensed indication for Flutiform was stated on the front page of the leavepiece and before any mention of Seretide. In addition, the licensed age ranges for Flutiform were stated twice on the front page of the leavepiece. There was, therefore, no confusion about the group of patients to which this whole leavepiece was relevant. Readers would only consider prescribing in this patient group and Napp therefore refuted the allegation that the claims were misleading; patient safety was not in doubt.

Napp noted that the therapeutic indications of the two products were almost identical and so in that regard it was entirely reasonable to present therapeutic options, within the licensed indication.

In response to the comment that clinically important differences between the marketing authorizations for Flutiform and Seretide Evohaler misled the prescriber, Napp maintained its position that the leavepiece did not suggest that all existing patients might be switched to Flutiform. Moreover, the leavepiece did not specifically advocate that existing Seretide Evohaler patients be switched and could include new asthma patients not adequately controlled (in accordance with the licensed indications).

Many factors that influenced prescribing decisions. Napp noted GlaxoSmithKline's submission that the inclusion of ethanol as an excipient was an important

influencing factor for prescribing but disputed that the presence of such small amounts of it were a significant consideration in general prescribing. The ethanol content was negligible, it was within the mg range and below that which was a cause for concern (alcohol content below 100mg per dose was considered negligible by the EMA). To put this into context alcohol could be present naturally in small amounts in many foodstuffs particularly in ripened fruit and fresh (unpasteurised) fruit juice.

With regard to the ethanol content, Napp was uncertain about the specific ethnic groups to which GlaxoSmithKline had referred; many alcohol-containing asthma therapies were approved in countries with predominantly Muslim populations eg Fostair (Pakistan and Turkey) and Salamol (UAE). Those religions that prohibited the consumption of alcohol might tolerate the small amounts of alcohol used in medicines. Furthermore, many other pMDIs used in routine practice, for the treatment of asthma, contained small amounts of alcohol as an excipient, something which many doctors would know. For those rare situations where ethanol needed to be considered the information was available in the prescribing information and in the patient information leaflet (PIL). To illustrate the principle it was not a requirement or common practice to include specific mention of lactose as an excipient even though this made a medicine unsuitable for certain groups of patients, eg those allergic to lactose. Seretide Accuhaler (DPI) contained lactose as an excipient but it did not know of any GlaxoSmithKline marketing materials which explained this. Both Napp and GlaxoSmithKline patient information leaflets noted the alcohol and lactose excipients respectively.

Page 3 of the leavepiece stated that Flutiform was 'Licensed for use with an AeroChamber Plus Spacer', the prescribing information also clearly stated that 'the AeroChamber Plus spacer device is recommended in patients who find it difficult to use inhalers'. Therefore, when making a clinical decision, the fact that Flutiform was only recommended for use with the AeroChamber Plus was made clear. If the clinician wished to use a spacer, that option was available with the AeroChamber Plus, so the prescriber could use the information provided to make an informed decision about the most appropriate product for their patient.

Napp submitted that it had not omitted key information and denied breaches of Clauses 7.2, 7.3, or 7.4.

PANEL RULING

The Panel noted that both the heading and subheading to page 2 referred to prescribing Flutiform 'instead of Seretide Evohaler'. The subsequent bullet points explained why, in Napp's view, Flutiform should be so prescribed. No information was given about when such a substitution would be appropriate. The Panel noted that Flutiform was not a suitable substitute for patients aged between 4 and 11 years who could be treated with Seretide Evohaler. The Panel noted its comment above at Point 1 that many readers would already be familiar with Seretide Evohaler. The Panel considered that in the absence of information to the contrary, readers would assume that Flutiform could be substituted for Seretide Evohaler in all circumstances and that was not so. The information about Flutiform's licensed indication in relatively small print on page 1 was insufficient to negate the unequivocal impression given by page 2. The Panel considered that page 2 was misleading and incapable of substantiation on this point. A breach of Clauses 7.2, 7.3 and 7.4 was ruled.

4 Claim 'Faster onset of action (P<0.001; secondary endpoint)'

This claim appeared on page 2 of leavepiece 1 immediately beneath the bullet point at issue at Point 1 above, 'Comparable clinical efficacy'. The claim was referenced to Bodzenta-Lukaszyk (2011a).

COMPLAINT

GlaxoSmithKline stated that 'Faster onset of action' was presented in both leavepieces as the key differentiator between Flutiform and Seretide Evohaler. The actual times to onset of action were not stated in the published paper, and importantly, it had not been established that a shorter time to onset of action was of value in a controller medicine. Furthermore, Napp did not provide any clinical evidence to substantiate the clinical relevance of this claim.

With regard to the clinical relevance of the claim, in inter-company dialogue Napp had hypothesised that 'Faster onset of action' might lead to improved patient preference and so improved adherence. However, the trend seen in the only head-to-head study Bodzenta-Lukaszyk *et al* (2011a) indicated that the onset of action difference became less apparent as time progressed, thus any purely theoretical benefit would presumably manifest in the early stage of therapy. This was, however, not substantiable as the evidence actually contradicted such a hypothesis. The data showed that patients significantly favoured Seretide (Odds ratio 0.495 CI 0.289, 0.848) over Flutiform with no significant difference presented in adherence rates to study medication. Napp's own data thus negated such a hypothesis.

GlaxoSmithKline stated that in leavepiece 1 the claim 'Faster onset of action' appeared on the same page and next to the bold claim 'flutiform is licensed for maintenance therapy and not for acute symptom relief'.

A claim for a faster onset of action was typically synonymous with a reliever (or SMART [Symbicort Maintenance and Reliever Therapy]) therapy and could, potentially, lead to inappropriate off-label use of Flutiform inconsistent with its SPC and pose risks to patient safety.

GlaxoSmithKline maintained that Napp had failed to substantiate the clinical relevance of this claim and the audience was not given appropriate information on which to assess the clinical relevance or impact of a faster onset of action in maintenance therapy with this controller medication. The juxtaposition

of claims in leavepiece 1 misled the reader and potentially encouraged Flutiform to be misused and prescribed off-licence. GlaxoSmithKline alleged that the claim was in breach of Clauses 3, 7.2 and 7.4.

RESPONSE

Napp submitted that the time to onset of action for formoterol was included in Section 5.1 of the Flutiform SPC, which stated that 'The onset of bronchodilating effect is rapid, within 1 - 3 minutes'.

Napp submitted that its accurate and objective data with regard to onset of action presented in leavepiece 1 was:

'Prescribe flutiform instead of Seretide Evohaler because it can deliver:

- Comparable clinical efficacy (P = 0.007; open label)
    - o Faster onset of action (P<0.001; secondary endpoint)'

The leavepiece stated a fact, substantiated by the results of a clinical trial that Flutiform had a faster onset of action (P<0.001; secondary endpoint) compared with Seretide (Bodzenta-Lukaszyk *et al* (2011a)). GlaxoSmithKline acknowledged this point during inter-company dialogue.

With regard to GlaxoSmithKline's specific concerns, Napp proposed during inter-company dialogue that the claim was included as the speed of onset of a LABA was an area of emerging clinical opinion as per Clause 7.2. Napp submitted that as discussed in inter-company dialogue, it was relevant to highlight the differences in onset of action between Flutiform and Seretide Evohaler as it was a key differentiator between LABAs and of clinical relevance for asthma maintenance therapy. GlaxoSmithKline would know from its own clinical development programme for fluticasone furoate/vilanterol that the speed of onset of a LABA was a clinically relevant measure.

The difference in time to onset of action between formoterol and salmeterol was frequently identified and referred to in the literature. Palmqvist *et al* (1999) stated:

'... Important pharmacological differences between these drugs have been documented in vitro and in patients. First, formoterol has a faster onset of action compared with salmeterol, which has been documented both in airway smooth muscle preparations as well as in asthmatic patients.'

Napp submitted that other articles focussed almost entirely on this difference between formoterol and salmeterol (van Noord *et al* 1996 and Grembaile *et al* 2002). It was therefore, clearly a clinically interesting difference between the two combinations.

Napp noted that GlaxoSmithKline's clinical studies of fluticasone furoate/vilanterol vs fluticasone propionate/salmeterol and vilanterol vs salmeterol used onset of action as an endpoint, as determined by a 12% improvement (considered to be a minimal clinical difference (Santanello *et al* 1999), or 200ml improvement on day 0 and day 84 (clinicaltrials.gov). The fact that this was included within current GlaxoSmithKline clinical trials highlighted the fact that this was a clinically relevant measure. Napp further noted that Cazzola *et al* (2011) identified onset of action as an important criteria for creating any new LABA and this, coupled with the above studies, reinforced that rapid onset of action was a clinically relevant differentiator.

Napp submitted that diurnal rhythm dictated that pulmonary function was poorest in the early mornings and this natural diurnal variation was often exaggerated in patients with asthma (Hetzel and Clark 1980, Hetzel 1981 and Clark 1987). Rapid bronchodilation following the morning dose of maintenance medication might therefore benefit these patients. This was of clinical relevance to the reader of the leavepiece.

To highlight the importance of time to onset of action in maintenance therapy, the following references which were presented to GlaxoSmithKline in inter-company dialogue:

Bender *et al* (2007) described the results from a survey of adult patients with asthma about the factors which influenced their decisions about when to use their asthma controller medications. Adherent and non-adherent patients were asked about factors they perceived to be important for maintenance therapy. Many patients, and particularly the non-adherent patients, expressed a strong preference for medications that worked quickly.

Harding *et al* (2009) determined whether patient perceptions about onset of action were clinically meaningful. It was concluded that showing that patients could feel a maintenance inhaler therapy work right away was meaningful to clinical decision-making, and the attribute could potentially improve patient adherence with therapy.

Murphy and Bender (2009) reviewed patient perspectives and preferences for controller medications and discussed the importance of speed of onset of action for various treatment regimes. The review further supported the premise that onset of action was an area of emerging clinical and/or scientific opinion.

Leidy *et al* (2009) stated that 'Feeling a maintenance therapy work right away may provide positive reinforcement and may offer one way to improve adherence in patients with asthma'. The authors further stated: 'Most patients reported that feeling their medication work right away is reassuring and would help them manage their asthma'.

Leidy *et al* (2008) outlined the process of developing a test to assess patient perception and satisfaction with feeling an asthma medication working right away. The authors stated 'A maintenance medication that patients with asthma can feel working shortly after administration could reinforce daily treatment and improve satisfaction, adherence, and outcomes'.

Hauber *et al* (2009) quantified the relative importance that patients who used combined ICS/LABA

maintenance medication placed on onset of action. The authors concluded 'Patients with asthma have clear preferences for perceived onset of effect in maintenance medications ... may increase the use of and adherence to maintenance medications'.

Napp further referred to the following peer-reviewed articles from its own studies that further supported for the importance of onset of action.

Thomas *et al* (2011) discussed physicians' attitudes towards the effectiveness of different single- or dual-inhaler combinations of an ICS and a LABA in the context of asthma management, including reasons for their choice. The most common reason for selecting a given combination was rapid onset of action (60%) followed by high potency of the steroid (39%).

Bousquet *et al* (2012) reported on a Delphi process to determine attributes perceived to be important in the selection of combination therapy followed by a pan-European survey to assess the attitudes, perceptions and prescribing behaviour of a larger population of physicians with a specialist interest in asthma treatment. Both the Delphi process stage and the pan-European survey showed that onset of action was one of the most important aspects for an ICS/LABA combination.

Napp noted that GlaxoSmithKline had also raised concerns that the onset of action difference became less apparent as the study progressed, thus any purely theoretical benefit would presumably manifest in the early stages of therapy. Napp had addressed this in inter-company dialogue. The fact that the size of the difference reduced over the course of the study was entirely expected as control improved, leaving less room for improvement. The telling point was the fact that the faster onset could still be demonstrated, even after three months of maintenance therapy once near-maximal improvements in FEV1 had been reached.

Napp had further characterised the faster onset of action seen both at the beginning of the head-to-head study, and after 12 weeks in post hoc analysis. Aalbers *et al* (2012) confirmed and expanded on the results from the head-to head study, Bodzenta-Lukaszyk *et al* (2011a), highlighting that Flutiform had a faster onset of action at all study visits.

Interestingly, assessment of patient perceptions of onset of action also showed that patients could perceive a difference between combinations containing either formoterol or salmeterol (O'Conner *et al* 2010).

Napp submitted that the suggestion that the results of a patient assessment of medication endpoint negated any other hypothesis was clearly not valid. The endpoint was exploratory and came from a non-validated question and was not sourced from any established questionnaire; it captured the response to the question 'How was the study medication at treating your asthma?' and had a five-point scale for response. Data were captured at end of study and would reflect overall experience with medication and not the benefit of a rapid bronchodilation.

To assess the benefit to patients of a faster bronchodilation would require more specific validated questionnaires such as the 5-item Onset of Effect Questionnaire (OEQ) which was not included in this study (Hauber *et al* 2009).

Napp also noted that in the context of a clinical trial the patient assessment of medication was 'very good' or 'good' for 84% of patients treated with Flutiform and 91% treated with Seretide at Day 84. Both treatments were therefore rated highly, and only 1% in each group scored either device as 'very poor'. However, this might not be reflected in the real world setting where patients were not frequently reviewed by a health professional. The link that GlaxoSmithKline had tried to make between two different endpoints, namely speed of onset of action and patient satisfaction, was still not clear, and did not negate this response and that provided during inter-company dialogue.

For these reasons, Napp submitted that the claim was substantiated. Onset of action was of clinical interest for a maintenance therapy, and therefore a relevant point to mention. Napp denied breaches of Clauses 7.2 and 7.4.

Napp submitted that the juxtaposition of the claims 'Faster onset of action' and 'flutiform is licensed for maintenance therapy and not for acute symptom relief' was appropriate and deliberate to clearly highlight that Flutiform was licensed for maintenance therapy and not for acute symptom relief despite its relatively fast onset of action. Napp considered it necessary to include such text to ensure that prescribers were clear that although Flutiform included formoterol (the same LABA included in Symbicort and Fostair which could both be used as maintenance and reliever therapy) it was only licensed for use in maintenance therapy and that any use for acute symptom relief would be off-licence. Napp therefore denied a breach of Clause 3 as it had clearly indicated in large font that Flutiform was licensed for maintenance therapy and not for acute symptom relief.

Napp submitted that it had substantiated the clinical relevance of the claim and provided appropriate information as part of the inter-company dialogue. The juxtaposition did not mislead the reader and so did not encourage off-licence use of Flutiform. Napp denied a breach of Clauses 3, 7.2 and 7.4.

PANEL RULING

The Panel noted GlaxoSmithKline's submission that the claim 'Faster onset of action' appeared in both leavepieces. It did not appear in leavepiece 2 and thus the Panel made no ruling in relation to that leavepiece.

The Panel noted both parties' submissions about the clinical relevance of the claim. In particular, the Panel noted the studies submitted by Napp indicated overall that onset of action was of clinical interest and relevance for a maintenance therapy. The claim was not misleading or incapable of substantiation on this point. No breach of Clauses 7.2 and 7.4 was ruled.

The Panel noted that alongside the bullet points, including that at issue above, was an image of a Flutiform pMDI beneath which and in the bottom left-hand corner of the page, was the prominent claim 'flutiform is licensed for maintenance therapy and not for acute symptom relief'. The Panel did not consider that the juxtaposing of the claim 'Faster onset of action' and the description of its licensed use for maintenance therapy misled the reader as alleged or promoted it in a manner that was inconsistent with its marketing authorization. The page made it clear that Flutiform was licensed for maintenance therapy. The Panel further noted that the claim was within the context of 'Why should I prescribe flutiform instead of Seretide Evohaler?'. The Panel considered that prescribers would be familiar with Seretide and know that it was only indicated as a maintenance therapy. No breach of Clauses 3.2 and 7.2 was ruled.

During its consideration of this matter the Panel noted that leavepiece 2 featured the closely similar claim 'The same inhaled steroid combined with a faster-acting LABA' referenced to Bodzenta-Lukaszyk (2011a). Although this particular claim was not cited by GlaxoSmithKline the Panel queried whether it would be caught by the ruling on this point and requested that Napp be advised of its concern in this regard.

5 Cost-effectiveness claims

The fourth bullet point on page 2 of leavepiece 1 beneath the heading 'Prescribe flutiform instead of Seretide Evohaler because it can deliver:' read 'Improved cost-effectiveness'. Page 3 featured a table which compared the acquisition costs of Flutiform and Seretide Evohaler.

Leavepiece 2 was headed 'Flutiform (fluticasone propionate/formoterol fumarate) inhaler as a cost-effective treatment for asthma management' and discussed the economic burden of asthma and the recommendation from the National Institute for Health and Care Excellence (NICE) to prescribe the least costly combination device with Seretide Evohaler accounting for 43% of these inhalers. A subsequent section headed 'Rationale for flutiform' claimed that 'flutiform provides the clinician with a cost-effective treatment choice when ICS/LABA combination inhalers are being considered at Steps 3 or 4 of the SIGN/BTS guidelines'. A chart of potential annual acquisition cost savings followed within a separate section.

The claims for 'cost-effective' or delivering 'Improved cost-effectiveness' were referenced to 'Data on file. – Flutiform cost-effectiveness analysis'.

COMPLAINT

GlaxoSmithKline noted that the supplementary information to Clause 7 stated:

'The economic evaluation of medicines is a relatively new science. Care must be taken that any claim involving the economic evaluation of a medicine is borne out by the data available and does not exaggerate its significance. To be acceptable as the basis of promotional claims, the assumptions made in an economic evaluation must be clinically appropriate and consistent with the marketing authorization.'

GlaxoSmithKline stated that the data cited in support of the claims at issue most closely resembled a cost-minimisation analysis which of itself required robust evidence for clinical equivalence with respect to patient outcomes. In this instance, the cost-minimisation analysis assumed that the health benefits of Seretide and Flutiform were 'similar' and then dismissed efficacy, and the resultant analysis focussed entirely on costs.

GlaxoSmithKline stated that there was no randomised, double-blind, head-to-head study which compared Seretide Evohaler and Flutiform. The only comparison between the two was a 12 week, open label, non-inferiority study investigating the low and medium doses in adults using a spacer device (Bodzenta-Lukaszyk *et al* 2011a). As highlighted earlier, the primary endpoint of the trial was non-inferiority of FEV1. High doses of Seretide and Flutiform had not been compared and studies of high dose were an essential prerequisite to establish comparable safety with any degree of certainty.

The clinical efficacy proven with Seretide had demonstrated guideline-defined control (which included the following asthma outcomes: PEF, rescue medication use, symptoms, night-time awakenings, exacerbations emergency visits, and adverse events) over a 12 month period in the GOAL study. Therefore, the assumption of comparable clinical efficacy for the basis of the cost-minimisation analysis could not be justified.

Furthermore, there were a number of issues with the methodology and assumptions used within the analysis. These had been highlighted by GlaxoSmithKline in inter-company dialogue but not addressed by Napp. A summary was provided below:

- Fostair was included in the cost-minimisation analysis, however, no mention of how clinical equivalence with Fostair was established prior to the subsequent cost analysis. There were no head-to-head clinical trials comparing Flutiform and Fostair.
- Fostair could also be used at a dose of 1 puff twice daily and cost less than Flutiform at the lowest dosing level. In addition Seretide 500 Accuhaler cost less at the highest dosing level. Both of these pertinent clinical possibilities had been excluded from the analysis.
- There were some patients who could not be switched to Flutiform or who would require additional consultation and prescription costs who had not been accounted for in the analysis (eg patients who used a Volumatic Spacer or who were unable to use inhalers containing ethanol)
- Consultation costs or the consequences of worsening asthma control in the absence of a consultation were not incorporated within the analysis or within the potential savings within the leavepiece itself.

GlaxoSmithKline alleged that the above claims were not fair, accurate or balanced. The cost comparisons made were misleading and not substantiated by the cited reference. Breaches of Clauses 7.2, 7.3 and 7.4 were alleged.

RESPONSE

Napp submitted that in order to determine whether a medicine was cost-effective, several forms of economic evaluation could be undertaken. The main difference between the different types of evaluations was in how the benefits were measured and valued as stated by Drummond *et al* (1997):

Cost-effectiveness analysis – '… analyses, in which costs are related to a single, common effect'

Cost-benefit analysis – 'Analyses that measure both the costs and consequences of alternatives in monetary units'

Cost-utility analysis – 'Analyses that employ utilities as a measure of the value of programme effects'

Cost-minimisation analysis – 'Where the consequences of two or more treatments or programmes are broadly equivalent, so the difference between them reduces to a comparison of cost'.

Napp maintained that Flutiform had demonstrated 'comparable clinical efficacy' to Seretide Evohaler and was 'broadly equivalent' and so a cost-minimisation analysis was an appropriate form of economic evaluation. Only medicine costs were compared and the cheapest intervention would provide the best value for money and was therefore deemed to be a cost-effective treatment option. Given Flutiform had lower costs than Seretide Evohaler, it was a cost-effective treatment option.

In generating the model, the results of non-inferiority trials were accepted as the basis for cost-minimisation analyses, as stated by Haycox and Walker (2009).

'... with many cost-minimisation analyses being based on trials that were not specifically designed to prove clinical equivalence. Many sources of clinical evidence can be used to support economic evaluations; however the "gold standard" is normally considered to be the RCT [Randomised Control Trial]. Such trials can be subdivided into superiority trials, equivalence trials and, as has been done more recently non-inferiority trials.'

Additionally, Flutiform was evaluated by the Scottish Medicines Consortium (SMC) following an abbreviated submission. Based on the evidence submitted, the SMC accepted Flutiform for use and stated:

'[Flutiform] has demonstrated clinical non-inferiority to another combination product containing a corticosteroid and long-acting β2-agonist and may offer cost savings.'

The SMC accepted Flutiform for use based on the study in question and a cost-minimisation model and Napp submitted that this supported the cost-effectiveness statements. Reviews had also been published by PrescQIPP (December 2012) and the Midlands Therapeutics Review & Advisory Committee (September 2012) in support of Flutiform cost-effectiveness.

Napp disagreed with GlaxoSmithKline's statement that cost-minimisation analysis could only be used when there was 'robust evidence of clinical equivalence'. The head-to-head study of Flutiform and Seretide Evohaler was a randomised, control led, non-inferiority trial (Bodzenta-Lukaszyk *et al* 2011a). Napp noted that GlaxoSmithKline had again referred to the proven clinical efficacy of Seretide in the GOAL trial, without clearly explaining that this trial was for Seretide (DPI) Accuhaler and not the Evohaler.

The Napp data on file was cited to substantiate the claims in the leavepieces and as there were no comparisons with Fostair or Seretide Accuhaler within the materials, Napp was not clear how relevant GlaxoSmithKline's comments were on this. However, to answer the specific points raised Napp referred to the following:

i. Fostair was included in the cost-minimisation analysis, however, no mention of how clinical equivalence with Fostair was established prior to the subsequent cost analysis. There were no head-to-head clinical trials comparing Flutiform to Fostair.

The relevance of this comment to the materials at issue was unclear. The leavepieces specifically discussed the potential for use of Flutiform in place of Seretide Evohaler. Further, the data on file itself clearly stated at the outset that 'No direct comparative studies between [Flutiform] and [Fostair] have been conducted'.

ii. Fostair could also be used at a dose of 1 puff twice daily and cost less than Flutiform at the lowest dosing level. In addition Seretide 500 Accuhaler cost less at the highest dosing level. Both of these pertinent clinical possibilities had been excluded from the analysis.

Again, the relevance of this comment to the material at issue was unclear. Neither Fostair nor Seretide Accuhaler were discussed within the leavepieces.

iii. There were some patients who could not be switched to Flutiform or who would require additional consultation and prescription costs which had not been accounted for in the analysis (eg patients who used a Volumatic Spacer or who were unable to use inhalers containing ethanol).

Napp noted that it had already discussed the issues surrounding the use of a Volumatic spacer and inhalers containing ethanol (Point 3 above). The data on file clearly set out how the figures used within the cost-minimisation analysis were calculated:

'Scottish Prescription Cost Analysis (PCA) was used to find the market share of the chosen MDIs in Scotland. These dispensed quantities are for all ICS/LABA combination units dispensed in primary care for both asthma and COPD. Cegedim Strategic Data (CSD) was used to ascertain the percentage of inhalers for [Seretide] and [Fostair] for asthma only and for patients over the age of 12 (comparable to low- and mid-dose [Flutiform]) and patients over the age of 18 (comparable to high-dose [Flutiform]). This is in line with the licensed indication for [Flutiform].'

iv. Consultation costs or the consequences of worsening asthma control in the absence of a consultation were not incorporated within the analysis, nor within the potential savings within the leavepiece itself.

Napp noted that cost-minimisation analysis was defined as:

'Where the consequences of two or more treatments or programmes are broadly equivalent, so the difference between them reduces to a comparison of cost'.

Consequently only medicine costs were included in subsequent calculations. Napp also noted that leavepiece 2 clearly stated the '**Potential** savings per annum' (emphasis added).

In summary, Napp considered that the claims were fair, accurate and balanced. Cost-effectiveness had been demonstrated and cost-minimisation analysis had been appropriately applied using medicine cost savings. The claims were substantiated and were not in breach of Clauses 7.2, 7.3 and 7.4.

PANEL RULING

The Panel noted that the claims at issue were referenced to Napp's data on file (UK/FLUT-12067 August 2012. HTA submission to support the cost-effectiveness of fluticasone propionate/formoterol fumarate MDI (metered-dose inhaler)) which Napp described as a cost-minimisation study. Only acquisition costs were compared. The Panel noted each party's submission on whether Bodzenta-Lukaszyk *et al* (2011a) demonstrated comparable efficacy and thus whether a cost-minimisation study was the appropriate analysis. In particular, the Panel noted that the study was an open-label, non-inferiority study; it had not been designed to demonstrate equivalence. The Panel also noted its rulings and comments above at Points 1 and 2 about Bodzenta-Lukaszyk *et al* (2011a) about patients' ages, doses and asthma severity. The Panel queried whether a cost-minimisation analysis was therefore appropriate.

The Panel noted that cost-minimisation studies were a legitimate activity, nonetheless any claims derived therefrom had to clearly reflect the analysis and not otherwise be misleading. The Panel considered that a reader would expect the claim 'cost-effectiveness' in the absence of further qualification, to mean more than a simple comparison of acquisition costs. In each leavepiece subsequent and distinct sections discussed comparative acquisition costs thus compounding the impression that 'cost-effectiveness' was different and broader than a simple cost comparison. In leavepiece 2 the first bullet point about the economic burden of asthma referred both to the overall annual cost to the NHS of £1billion and the 'estimated annual drug cost for asthma' of £115million, thus highlighting the impact of indirect costs.

The Panel considered that the claims 'Improved cost-effectiveness' in leavepiece 1, '... a cost-effective treatment for asthma management' and '... a cost-effective treatment choice ...' in leavepiece 2, each implied that matters broader than acquisition cost had been compared. In addition the Panel noted its concerns about the cost-minimisation study and its reliance on Bodzenta-Lukaszyk *et al* (2011a) as set out above. The claims were thus each misleading and incapable of substantiation. Breaches of Clauses 7.2, 7.3 and 7.4 were ruled in relation to each.

6 Cost claims

Leavepiece 2 contained the claims 'cost-effective treatment for asthma management' and 'a cost-effective treatment choice when ICS/LABA combination inhalers were being considered at Step 3 or 4 of the SIGN/BTS guidelines'. The Napp data on file was cited in support of both.

COMPLAINT

GlaxoSmithKline submitted that there was a range of other products and devices available for 'asthma management' and at 'Step 3 or 4 of the BTS/SIGN guidelines'. These had not been included within the leavepiece, nor were they included within the Napp data on file cited in support of the claims. This was of particular relevance as some of these products cost less than Flutiform.

GlaxoSmithKline submitted that the leavepiece advised switching. The switching of inhaled medication and inhalers was a complex process as it involved reviewing and educating the patient on the technique required for operating the new inhaler effectively. It also required a further follow-up review of the patient to ensure not only that asthma control was maintained but also that the patient was able to continue to use the inhaler properly.

No evidence was presented in the leavepiece to demonstrate that asthma control was maintained if/when patients were switched. Consequently the claims for potential annual savings did not take into account the costs associated with the necessary additional clinical interactions required with patients when they had their medicines changed or the potential costs associated with the risk of any resultant exacerbations.

In addition, the data presented were stratified by age; however, there were many patients who could not be switched to Flutiform who had not been considered eg patients who used a Volumatic spacer or those who were unable to use inhalers containing ethanol. Furthermore, the Napp data on file did not include

the full range of products and devices and thus could not substantiate the above claims. GlaxoSmithKline thus alleged that the claims and the accompanying table were in breach of Clauses 7.2 and 7.3.

RESPONSE

Napp stated that leavepiece 2 referred to Flutiform as a 'cost-effective treatment for asthma', and that it 'provides the clinician with a cost-effective treatment choice when ICS/LABA combination inhalers are being considered at Steps 3 and 4 of the SIGN/BTS guidelines'. These statements were supported by the results of the Napp cost-minimisation model.

It was entirely appropriate to use Seretide Evohaler as the comparator within the table for the following reasons:

- Seretide Evohaler was a widely used pMDI in the UK
- Flutiform and Seretide Evohaler had been directly compared in a clinical study.

As discussed in Point 5 above, cost-minimisation analysis was defined as: 'Where the consequences of two or more treatments or programmes are broadly equivalent, so the difference between them reduces to a comparison of cost.' Consequently, only medicine costs were included in the calculations. Napp submitted that its data on file clearly set out how the figures used within the cost-minimisation analysis were calculated.

Napp submitted that leavepiece 2 did not use the words 'drug switching', although the licensed indication was presented as part of the introduction to Flutiform. This included the possibility of prescribing Flutiform to either new patients not adequately controlled on their existing medication or for existing patients on Seretide Evohaler or another appropriate ICS/LABA combination (ie switch). Napp acknowledged that switching inhalers might not be simple and might have associated indirect costs incurred by clinical interactions or increased exacerbations. However, there might also be additional savings above those simply due to the cost of the inhaler, including reduced clinical interactions, and reduced exacerbations as a result of improved asthma control on switching. Hence Napp had been careful to state potential cost savings in leavepiece 2, and not advocate either starting all new asthma patients (inadequately controlled) or switching patients to Flutiform from another ICS/LABA inhaler.

With regard to patients using a Volumatic spacer device and patients unable to use inhalers containing ethanol, Napp referred to its response to Point 3 above. Napp also noted that there was no assumption within the leavepiece that all patients would be switched from Seretide Evohaler to Flutiform. Importantly the table looked at 25%, 50% and 75% of inhalers moving to Flutiform and did not include a 100% column. The table analysed potential cost-savings if patients switched, therefore it did not advise general switching.

Napp therefore submitted that the potential savings in the table were not misleading. The table clearly stated potential cost savings and was clearly labelled to define that the saving referred to medicine costs, by labelling the medicine and the cost.

In conclusion, using Seretide Evohaler as a comparator was justified, Napp did not assume all patients could switch and the table was factually accurate and not misleading. There was no breach of Clauses 7.2 or 7.3.

PANEL RULING

The Panel noted GlaxoSmithKline's allegation that the claims '... cost-effective treatment for asthma management' and 'a cost-effective treatment choice when ICS/LABA combination inhalers are being considered at Steps 3 or 4 of the SIGN/BTS guidelines' were misleading as other relevant products, some of which were less expensive than Flutiform, were not included in the Napp data on file analysis. This allegation had not been considered at Point 5 above.

The Panel noted that the heading of leavepiece 2 was a broad unqualified claim that Flutiform was a cost-effective treatment for asthma management when compared with all other relevant products. The comparison was not limited to that with Seretide Evohaler. The Panel noted its general comments on this claim at Point 5 above. The Panel considered that the heading 'flutiform...as a cost-effective treatment for asthma management' was misleading as alleged on this narrow point and a breach of Clause 7.2 was ruled.

The Panel noted that the claim 'flutiform provides the clinician with a cost-effective treatment choice when ICS/LABA combination inhalers are being considered at Steps 3 or 4 of the SIGN/BTS guidelines' was the sole bullet point in a section headed 'Rationale for flutiform'. The Panel noted the heading of leavepiece 2 and its comments thereon above and did not consider that the section in question was necessarily limited to a comparison with Seretide Evohaler as inferred by Napp; Seretide was not the only other ICS/LABA combination inhaler which could be used at Steps 3 or 4 of the SIGN/BTS guidelines. In the Panel's view the claim in question implied that Flutiform was a cost-effective choice when compared with all other ICS/LABA combination inhalers used at Steps 3 or 4 of the guidelines. It was not limited to a comparison with the Seretide Evohaler as alleged and was misleading in this regard. Breaches of Clauses 7.2 and 7.3 were ruled.

The Panel noted that the table within the section headed 'Potential savings per annum' compared the cost savings, based on acquisition costs if 25%, 50% or 75% of patients on Seretide Evohaler 50, 125 and 250 were switched to Flutiform. In the Panel's view the table did not advocate switching *per se* as alleged by GlaxoSmithKline. It merely set out the potential savings based on acquisition costs in the event of a switch to the Seretide Evohaler. In the Panel's view, the basis of the comparison was clear and was not misleading as alleged. No breaches of Clauses 7.2 and 7.3 were ruled.

7 Table headed 'Can flutiform offer a range of strengths and savings?'

Page 3 of leavepiece 1 was headed 'Can Flutiform offer a range of strengths and savings?', and featured the table below.

	flutiform (fluticasone/ formoterol)		Seretide Evohaler (fluticasone/ salmeterol)		flutiform Drug cost savings
	Strength	Cost	Strength	Cost	
High	250/10ug	£45.56	250/25ug	£59.48	£13.92
Medium	125/5ug	£29.26	125/25ug	£35.00	£5.74
Low	50/5ug	£18.00	50/25ug	£18.00	£0.00

COMPLAINT

GlaxoSmithKline stated that in leavepiece 1 a claim of cost-effectiveness lay adjacent to a cost comparison of the three different strengths of Seretide Evohaler and Flutiform. Cost-effectiveness compared with Evohaler had not been demonstrated as discussed at Point 6 above. Given that cost-effectiveness had not been demonstrated, the juxtapositioning of this statement next to a cost comparison table that was itself not balanced, was misleading.

The cost comparison table only compared Flutiform with Evohaler. GlaxoSmithKline noted that alternative products were also available: Seretide Accuhaler (salmeterol/ fluticasone, GlaxoSmithKline), Symbicort (budesonide/ formoterol, AstraZeneca) and Fostair (beclomethasone/ formoterol, Chiesi) were also indicated for the maintenance treatment of asthma at Step 3 and 4 of the BTS/SIGN guidelines. Furthermore, the omission by Napp of the Seretide Accuhaler prices, particularly the high strength, appeared deliberate to conceal the fact that the Seretide 500 Accuhaler was a less expensive alternative to Flutiform 250/10µg.

In inter-company dialogue, Napp submitted that the Seretide Evohaler was the most appropriate comparator because clinical data vs Seretide Evohaler had been presented within leavepiece 1. GlaxoSmithKline disagreed with Napp's position and noted that the appropriate information referenced to Bodzenta-Lukaszyk *et al*, (2011a) for the mid/ low doses comparisons was missing from the cost comparison table The reader was thus unaware that the rationale for this cost comparison was based solely upon non-inferior FEV1 results over a 12 week period in adults.

Whilst GlaxoSmithKline acknowledged that Napp's rationale for only directly comparing the two products, when other products were available, was because head-to-head data existed, it must be clearly acknowledged that data only existed for the low and medium doses of the inhaler, in 18 year olds and in an open label study that did not include severe patients.

As previously highlighted, Seretide Evohaler and Flutiform differed in many aspects; licensed age ranges, alcohol content and spacer device usage. None of these had been made clear within leavepiece 1 which implied that all patients could be prescribed Flutiform instead of Seretide Evohaler. Clearly, this was not the case and Napp was obliged to present these important differences in a fully transparent and balanced way.

In summary, GlaxoSmithKline alleged that the cost comparison table was misleading, not accurate, fair or balanced and in breach of Clauses 7.2 and 7.3.

RESPONSE

Napp submitted that it had already explained in responses to Points 2, 4, 5 and 6 above that Flutiform had comparable clinical efficacy, was cost-effective and an appropriate option for use instead of Seretide Evohaler.

Positioned under the title header 'Can flutiform offer a range of strengths and savings?', the table clearly demonstrated the range of Flutiform's strengths and its respective costs, which were juxtaposed against the common details of Seretide Evohaler, with a further adjacent column clearly titled 'flutiform Drug cost savings'.

Seretide Evohaler and its range of strengths (and consequent pricing) was specifically chosen and placed against the entries of Flutiform, as it was rational that Flutiform and its range of strengths (and consequent pricing) should be placed in the most appropriate clinical context in the table by juxtaposing it with its most similar product, ie a medicine used for the same needs or intended for the same purpose. It was further appropriate, for the following reasons, to juxtapose specifically Seretide Evohaler against Flutiform, as there was direct clinical comparative data available and both were pMDIs, had three clinical doses, contained the same labelled dose of fluticasone and had dose counters.

It was also important in the context of savings to the NHS and clinicians that the Seretide Evohaler was the most commonly prescribed ICS/LABA combination pMDI in the UK and had cost the NHS over £300 million per annum for each of the last five years. This further strengthened the case for Seretide Evohaler's inclusion in the table set in the context against the Flutiform range, as cost was a highly relevant consideration for prescribers.

With regard to the other potential/possible inhalers that had been suggested for inclusion in the table, in addition to the fact that Napp did not have comparative evidence, Napp noted the following:

- Fostair was only available in one strength and in two treatment doses and so could not be appropriately set out as it stands in the current table against Flutiform and its full range of clinical doses. Thus, Fostair had not been included in the table.
- Seretide Accuhaler was a DPI which was a totally different delivery device system and required a different technique for inhalation. Seretide Accuhaler also only required one puff for dosing in contrast to the two puffs needed for

Flutiform dosing. In addition and importantly, Seretide Accuhaler was indicated not only for the treatment of asthma, but also for chronic obstructive pulmonary disease (COPD). Napp considered that these fundamental differences between Flutiform and Seretide Accuhaler, namely in the device delivery system, inhalation technique, dosing regimen, and in therapeutic indications, were significant enough for clinicians to perceive these two inhalers as two distinctly different medicines for use in different clinical contexts. Therefore, Napp considered that the inclusion of Seretide Accuhaler in the current table would be inappropriate, and its inclusion would confuse the clinician (and ultimately the patient). Thus, Seretide Accuhaler had not been included in the table;

- For similar reasons, Symbicort (a DPI) had not been included in this table, as stated above for Seretide Accuhaler, namely differences in device design (pMDI vs DPI), inhalation technique, therapeutic indication (asthma only vs asthma and COPD) and dosing regimens (of which Symbicort additionally included a SMART licence). Thus, Symbicort had not been included in this table.

Lastly, the focus of the clinical data package as detailed in the leavepiece, was vs Seretide Evohaler and so Napp considered it was appropriate to show only Seretide Evohaler in this table. The addition of other, and distinctly different, inhaler medicines without any previous mention in the leavepiece would be inappropriate and confuse the clinician.

Napp had also addressed in other responses the age ranges and spacer device used for Flutiform in leavepiece 1. It was not implied in either leavepiece that all patients could be prescribed Flutiform instead of Seretide Evohaler. The factual and comparative data had been presented in a fair and balanced way.

In summary, Napp submitted that the information on page 3 of leavepiece 1 was accurate, clear and noteworthy, fair and balanced, and importantly, clinically relevant, and therefore not in breach of Clauses 7.2 and 7.3.

PANEL RULING

The Panel noted its rulings above at Point 5 in relation to the claim 'Improved cost-effectiveness'. That claim was a bullet point beneath a prominent subheading and page heading. It was not 'next to' the cost comparison table on the facing page as GlaxoSmithKline alleged, nor was it within that table's immediate visual field. The Panel, whilst noting its ruling at Point 5, did not consider that the position of the claim 'Improved cost-effectiveness' on page 1 in relation to the table on page 2 was, in itself, misleading as alleged. No breach of Clause 7.2 was ruled.

The Panel considered that the basis of the comparison in the table was clear, the acquisition costs of flutiform 250/10mcg/, 125/5mcg/, 50/5mcg were compared with those of Seretide Evohaler 250/25mcg, 125/25mcg and 50/25mcg. There was no implication that all patients could be prescribed Flutiform instead of Seretide Evohaler, as alleged. Nor was it unacceptable to directly compare the acquisition costs of products if the basis of that comparison was abundantly clear. The table was not misleading as alleged. No breach of Clauses 7.2 and 7.3 was ruled.

8 Claim 'flutiform has a simple dosing schedule administered as 2 puffs, twice daily'

The claim at issue appeared in leavepiece 1 beneath the table referred to in Point 7 above and was referenced to the SPC.

COMPLAINT

GlaxoSmithKline stated that the leavepiece compared both clinical and economic aspects of Seretide Evohaler and Flutiform. The claim at issue appeared directly below the table at issue above.

In a comparative leavepiece designed to present the reasons why Flutiform should be prescribed instead of Seretide, the juxtaposition of the above statement directly below a comparative table implied that Seretide's dosing schedule was not simple or not as simple as Flutiform. This was not the case as the dosing schedules for the two inhalers were the same.

The use of the term simple to describe a dosing schedule was both a promotional claim and a hanging comparison and therefore required substantiation. Alternative, simpler dosing schedules for asthma were available and indeed Seretide Accuhaler was prescribed as one puff twice a day. Napp did not provide evidence to demonstrate that patients viewed a dosing schedule of two puffs twice a day as being simple but, in inter-company dialogue, advised that 'It ... is a plain statement of fact in terms of the dosing schedule for Flutiform being simple'.

As a result, GlaxoSmithKline alleged that, within material which compared Seretide with Flutiform, claims of a simple dosing schedule for Flutiform when the dosing schedules were the same was misleading. Furthermore, as simpler dosing schedules were available, a claim of simple was not accurate or balanced, was misleading and in breach of Clauses 7.2, 7.3 and 7.4.

RESPONSE

Napp submitted that leavepiece 1 provided health professionals with factual statements about Flutiform (ie all of page 1, wording beneath inhaler image on page 2, and the three statements beneath table on page 3). Throughout inter-company dialogue Napp had disagreed with GlaxoSmithKline's suggestion that the entire contents of the leavepiece were comparative.

The claim 'Flutiform has a simple dosing schedule administered as 2 puffs, twice daily' was one of three factual statements positioned beneath the table on page 3 of the leavepiece entitled 'Can Flutiform offer a range of strengths and savings?'. There was no implication that the first fact (simple dosing schedule) was any different from the adjacent two

facts 'Each inhaler contains 30 days' supply, 120 actuations = 60 doses' and 'Licensed for use with an AeroChamber Plus Spacer' – indeed all three facts applied equally to Seretide Evohaler and Flutiform.

The Oxford English Dictionary (OED) defined 'simple' as:

- 'easily understood',
- 'plain, basic or uncomplicated in form, nature or design; without much decoration or ornamentation.'

Napp maintained that 2 puffs, twice daily was both easily understood and uncomplicated. The word 'simple' was an adjective. 'Simple' was not the comparative or the superlative when 'simpler [than]', or 'simplest' would be used.

There was not, as implied, a comparative statement to Seretide Evohaler, and Napp had not used a hanging comparison as alleged ie the word, 'simpler', was not used. Furthermore, Napp did not imply that the dosing schedule for Seretide Evohaler was in any way more complicated than the dosing schedule for Flutiform.

In the context of other asthma management regimes 2 puffs, twice daily of an inhaler was simple. Napp agreed with GlaxoSmithKline that Seretide Evohaler had the same simple dosing schedule.

In summary, Napp maintained that simple was not used as a comparison, there was no use of hanging comparisons, no use of the word 'simplest' or 'simpler [than]'. The definition of 'simple' was as given by the OED. Taken in context with the two factual statements placed immediately adjacent to it, Napp asserted that the use of 'flutiform has a simple dosing schedule administered as 2 puffs, twice daily', which included the word 'simple', was accurate, fair and balanced, and therefore was not in breach of Clauses 7.2, 7.3, and 7.4.

PANEL RULING

The Panel noted that the claim in question appeared in small print beneath the comparative table at issue in Point 7 which comprised most of the page. The Panel considered that the claim would be considered by readers in the context of the overall comparative message of the page and thus it implied that Seretide Evohaler did not have a simple dosing schedule and that was not so. Seretide Evohaler had the same dosing schedule as Flutiform. The claim was misleading in this regard and incapable of substantiation. A breach of Clauses 7.2, 7.3 and 7.4 was ruled.

The Panel considered that the claim indirectly compared the dosing schedule of Flutiform with Seretide Evohaler. The Panel therefore did not consider the claim was a hanging comparison as alleged. Nor was it misleading because other products with simpler dosing schedules were available as alleged by GlaxoSmithKline. The Panel considered that the claim in question was not misleading on these points as alleged. No breach of Clauses 7.2 and 7.3 was ruled.

9 Clauses 8.1, 9 and 2

COMPLAINT

GlaxoSmithKline submitted, given the totality of the multiple issues raised and unresolved through extensive inter-company dialogue, that collectively the two leavepieces disparaged Seretide in breach of Clause 8.1. In addition, given the seriousness and number of breaches, the failure to maintain high standards and the potential to encourage Flutiform prescribing outside the marketing authorization and impact upon patient safety, the two leavepieces constituted an additional breach of Clauses 2 and 9.1.

RESPONSE

Napp firmly believed that it had fully addressed the multiple issues raised by GlaxoSmithKline during inter-company dialogue as well as in this response. The two leavepieces did not disparage Seretide Evohaler and were not in breach of Clause 8.1. Napp submitted that it had maintained high standards and did not encourage the prescribing of Flutiform outside of its marketing authorization nor compromised patient safety. Napp vigorously asserted that it had not breached multiple clauses including Clauses 2, 3, 7.2, 7.3, 7.4, 8.1, or 9.1.

PANEL RULING

The Panel noted its rulings above of breaches and no breaches of the Code. Whilst some comparisons had been considered misleading, the Panel did not consider that they went beyond that and disparaged Seretide Evohaler. No breach of Clause 8.1 was ruled.

The Panel noted its rulings of breaches of the Code set out above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

Although noting its rulings above, the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was reserved to indicate particular disapproval of a company's material or activities. No breach of Clause 2 was ruled.

APPEAL FROM GLAXOSMITHKLINE

GlaxoSmithKline alleged, given the number of issues raised and unresolved through extensive inter-company dialogue and the number of breaches of the Code ruled by the Panel, that in addition to failing to maintain high standards, these two leavepieces also breached Clause 2.

As acknowledged by the Panel, the information within the leavepieces was insufficiently complete to be certain that the reader could accurately interpret the claims and thereby appropriately prescribe Flutiform within its marketing authorization:

Point 1

> '.....the Panel considered the broad unqualified claim "comparable efficacy" implied more than a measurement of FEV1'.

'The Panel considered that the broad unqualified claim "Comparable clinical efficacy (P=0.007, open label)" implied that Flutiform could be used in all of those patients for whom Seretide might be prescribed and that there was robust comparative clinical data in relation to all doses and patient populations and that was not so. The Panel noted that there was some comparative efficacy data but considered that insufficient information about the study had been provided to enable the reader to accurately interpret the claim which was consequently misleading and incapable of substantiation'

Point 3

'No information was given about when such a substitution would be appropriate. The Panel noted that Flutiform was not a suitable substitute for patients aged between 4 and 11 years who could be treated with Seretide Evohaler'. The Panel considered that in the absence of information to the contrary, readers would assume that Flutiform could be substituted for Seretide Evohaler in all circumstances and that was not so'

GlaxoSmithKline stated in relation to the Panel's comments above that:

- the absence of such key information did not enable the prescriber to make a fully informed decision regarding the appropriate prescribing of Flutiform for their patients
- the claims of clinical comparability had not been suitably qualified to represent the current level of evidence to allow the reader to accurately interpret the claims
- no information was provided to the prescriber to advise when substitution from one treatment to another would be appropriate
- in the absence of information to the contrary, readers would assume that Flutiform could be substituted for Seretide Evohaler in all circumstances and that was not so

not only posed a risk to patient safety, but pointed to the fact that Napp had promoted outside of the licensed indication for Flutiform.

GlaxoSmithKline contended that this, together with the twenty breaches of the Code ruled by the Panel, brought the industry into disrepute in breach of Clause 2.

COMMENTS FROM NAPP

Napp was very disappointed that GlaxoSmithKline had appealed the Panel's ruling of no breach of Clause 2 and queried its reasons for doing so, given the Panel's careful and detailed assessment.

Napp submitted that given the extent and duration of this complaint, for the sake of clarity, the history was as follows. In September 2012 Napp launched Flutiform onto the UK fixed-dose combination respiratory market, a market worth around £700 million per annum, dominated by GlaxoSmithKline with annual sales from Seretide Evohaler exceeding £300 million.

Napp submitted that prior to the launch of Flutiform, the leavepieces, together with other promotional materials, were pre-vetted by the MHRA; amendments were made and accepted. The MHRA reviewed the data sets relevant to GlaxoSmithKline's complaint and raised no significant concerns. The MHRA saw the final versions of the two leavepieces in question. This was important given GlaxoSmithKline's allegation that Napp had compromised patient safety and promoted outside of the Flutiform licence.

Napp submitted that within the first week of launch, GlaxoSmithKline had contacted Napp about leavepiece 2 (ref UK/FLUT 11023a), aimed at NHS payers, as it had significant cost savings over Seretide Evohaler at the medium and high doses. By the end of the second week of launch, GlaxoSmithKline had written to Napp about both of the leavepieces now at issue; the company challenged ten points and alleged twenty eight breaches of the Code.

Napp submitted that in the extensive inter-company dialogue which ensued, it made every effort to find a solution to the allegations. However GlaxoSmithKline only accepted Napp's proposed amendments in respect of two of the ten points. Furthermore, during inter-company dialogue GlaxoSmithKline failed to answer an important and relevant question about the licensed age ranges and device in its GOAL study and GlaxoSmithKline's Seretide promotional materials. GlaxoSmithKline stated that if Napp would like to raise the new point in a separate complaint, it would be happy to provide a detailed response. The significance of this was that Napp acted reasonably and tried to find an acceptable solution which GlaxoSmithKline would not entertain, despite the fact it did not make such matters clear in its own promotional materials.

Napp submitted that following unsuccessful completion of inter-company dialogue, GlaxoSmithKline introduced major new points contrary to the requirements of Paragraph 5.3 of the Constitution and Procedure. Notwithstanding GlaxoSmithKline's failure to follow due process, Napp discussed this with the PMCPA and agreed to respond, albeit within additional time which was needed given the new points raised. The Panel reviewed each company's arguments and made its rulings, which Napp had accepted and which GlaxoSmithKline had now appealed.

Napp noted that GlaxoSmithKline had appealed against the ruling of no breach of Clause 2 mainly because of the multiple issues raised and unresolved through extensive inter-company dialogue and the cumulative number of breaches of the Code. Napp vigorously disputed both of these points.

Napp submitted that to suggest that Clause 2 should be applied because of the number of issues 'unresolved through extensive inter-company dialogue' was illogical, as all inter-company complaints to the PMCPA should only occur after unresolved inter-company dialogue. If a matter was resolved through inter-company dialogue, then there would not be a complaint to PMCPA. Inter-company dialogue was a procedural step and the failure to

agree a matter at this stage in and of itself should have no bearing on whether Clause 2 had been breached.

Moving to GlaxoSmithKline's second reason 'cumulative number of breaches', Napp noted that the Panel had ruled breaches of Clauses 7.2, 7.3, 7.4 and 9.1 but no breaches of 2, 3.2 or 8.1. GlaxoSmithKline correctly stated that there were twenty breaches ruled, but ignored the fact that several of the breaches concerned the same matter (see below) and that the Panel also ruled against thirteen of GlaxoSmithKline's complaints. The twenty breaches related to eight grounds of complaint, of which two were found not to be valid and two were upheld in part only:

- For the claim 'comparable clinical efficacy' there were two breaches, each, of Clauses 7.2, 7.3 and 7.4
- For the claim 'the efficacy and tolerability of flutiform were sustained for up to 12 months' there was a breach of Clause 7.3
- For the question 'why should I prescribe flutiform instead of Seretide Evohaler?' there was a breach of Clauses 7.2, 7.3 and 7.4
- For the claim 'Faster onset of action' there was no breach of Clauses 3.2, 7.2, and 7.4
- For cost-effectiveness claims, breaches of Clauses 7.2, 7.3 and 7.4 were ruled
- For cost claims there was a breach of Clause 7.2 on a narrow point, breaches of Clause 7.2 and 7.3 and no breach of Clauses 7.2 and 7.3
- For the table headed 'Can flutiform offer a range of strengths and savings?' there was no breach of Clause 7.2 and no breach of Clauses 7.2 or 7.3
- For the claim 'flutiform has a simple dosing schedule administered as 2 puffs, twice daily' there was a breach of Clause 7.2, 7.3 and 7.4 but no breach of 7.2 and 7.3
- For Clauses 8.1, 9.1 and 2, there was a breach of Clause 9.1 but no breaches of Clauses 8.1 or 2

Turning to GlaxoSmithKline's specific points:

- Point 1 – The first quotation from the Panel provided was selective and did not properly summarise the entire position and ruling on comparable efficacy, as the Panel further noted that the secondary outcome data showed that Flutiform and Seretide were similar in a number of additional relevant efficacy measures.
- Point 1 – Again the second quotation failed to fully represent the Panel's opinion on the point under discussion.
- Point 3 – The focus on providing further clarity had been accepted by Napp, and Napp again noted that GlaxoSmithKline also did not make it clear in its materials – a point it failed to respond to when questioned during inter-company dialogue.

Napp noted the supplementary information for Clause 2, which stated that:

> 'A ruling of a breach of this clause is a sign of particular censure and is reserved for such circumstances.
>
> Examples of activities that are likely to be in breach of Clause 2 include prejudicing patient safety and/or public health, excessive hospitality, inducements to prescribe, inadequate action leading to a breach of undertaking, promotion prior to the grant of a marketing authorization, conduct of company employees/agents that falls short of competent care and multiple/cumulative breaches of a similar and serious nature in the same therapeutic area within a short period of time.'

Napp firmly refuted GlaxoSmithKline's allegation that it had promoted Flutiform outside of its licence and specifically noted that the Panel ruled no breach of Clause 3.2. No breach of Clause 4 (failure to disclose prescribing information and obligatory information) had been alleged which indicated that no pertinent safety information had been omitted. Furthermore, the Panel also ruled that Napp did not disparage the Seretide Evohaler and was therefore not in breach of Clause 8.1.

The multiple breaches of 7.2, 7.3, 7.4 and the single breach of 9.1 ruled by the Panel had been at a single point in time, related to very similar claims, and were not repeated occurrences.

Napp submitted that fundamentally the complaint was about the possibility that the claims in question could mislead the reader. The Panel's rulings of breaches of the Code indicated that in order to use the claims at issue, additional qualification/ clarification was needed and care with respect to juxtaposition of claims and font size was required. Although Napp never intended to make any promotional claims in breach of either the letter or the spirit of the Code, it accepted these rulings and thanked the Panel for its detailed review of its materials and arguments and understood that this had been a lengthy process. The Panel carefully considered and concluded on each point and articulated its decision and reasoning in full. Napp was therefore happy that the Panel's decision was considered and fair. The Panel was correct to rule no breach of Clause 2; Napp regretted that the Appeal Board now needed to expend time and effort in the appeal of this ruling.

FINAL COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline stated that the decision to appeal the Panel's ruling of no breach of Clause 2 was not taken lightly. After carefully considering the facts surrounding this complaint, GlaxoSmithKline alleged that Napp's activities posed a risk to patient safety. It was regrettable, that on this occasion, GlaxoSmithKline had considered it necessary to refer this matter to the Appeal Board.

GlaxoSmithKline did not agree that its quotations of the Panel's rulings were selective, as it clearly stated 'The Panel noted that there was some comparative efficacy data.....', and thus summarised the entire position of the Panel ruling with regard to secondary endpoints.

GlaxoSmithKline noted that during inter-company dialogue Napp had raised a point of clarification

with regard to GlaxoSmithKline's material. In order not to confuse matters, GlaxoSmithKline requested written details from Napp to enable it to appropriately assess the query and respond. However, GlaxoSmithKline did not receive this written response and was surprised that this matter had been raised with the PMCPA six months later, contrary to the requirements of Paragraph 5.3 of the Constitution and Procedure.

In addition GlaxoSmithKline noted the following statements made by Napp in its comments on the appeal:

- 'GlaxoSmithKline only accepted Napp's proposed amendments in respect of two of the ten points'

GlaxoSmithKline stated that the two claims referred to by Napp were: 'Fluticasone and Formoterol in a fixed dose combination' and 'A comparable range of strengths in a familiar yet modern MDI'.

During a teleconference, GlaxoSmithKline and Napp discussed both claims in detail and no such amendments were proposed by Napp; nor were such proposed amendments submitted to GlaxoSmithKline. In the spirit of inter-company dialogue, GlaxoSmithKline was prepared to accept Napp's initial response about these two claims, and neither of these points were escalated to the PMCPA. At present both claims still featured in a different leavepiece (ref UK/FLUT-11050). GlaxoSmithKline therefore contested Napp's suggestion that amendments were proposed or indeed made.

- 'GlaxoSmithKline introduced major new points'

GlaxoSmithKline stated that the points to which Napp referred related directly to the original complaint regarding the claim 'comparable clinical efficacy'. GlaxoSmithKline did not agree that new points were raised. The points in question challenged the bioavailability, clinical evidence to demonstrate comparable clinical efficacy, patient selection and dosage selection of Flutiform studies. GlaxoSmithKline reminded Napp that it originally referred to all of these points in its correspondence. All points discussed within GlaxoSmithKline's complaint were provided as rationale scientific arguments to substantiate its concerns with regard to this claim that Flutiform was 'clinically comparable' to the Seretide Evohaler. GlaxoSmithKline noted that some of its materials had been pre-vetted by the MHRA. However, the clinical data package which accompanied a newly launched medicine was substantial and could often be complex. Therefore as an industry that operated through self-regulation, it had a responsibility to ensure it maintained the high standards that were expected by patients, health professionals and society. It might be appropriate for a company to raise concerns about the activity of a fellow company and this was how it ensured continued self-regulation and continued to ensure high standards.

GlaxoSmithKline submitted that key information to enable prescribers to make fully informed decisions of the appropriate prescribing of Flutiform for their patients had been excluded and claims of clinical comparability had not been suitably qualified to represent the current level of evidence. Ultimately, these significant issues put patient safety at risk, which collectively, with twenty breaches of the Code ruled by the Panel, constituted a breach of Clause 2.

APPEAL BOARD RULING

The Appeal Board noted that, prior to the hearing, GlaxoSmithKline had notified the Authority that it wanted to withdraw its appeal. This was as a result of further inter-company dialogue. Napp subsequently confirmed its agreement that the appeal should be withdrawn. GlaxoSmithKline, however, had notified the Authority after it had received Napp's response to GlaxoSmithKline's appeal and thus in accordance with Paragraph 15.2 of the Constitution and Procedure, the appeal could not be withdrawn. Both parties were so advised. The Appeal Board further noted that, in response to questioning, both companies maintained their position that they would have wished the appeal to be withdrawn.

The Appeal Board was concerned about the multiplicity of breaches ruled in the two leavepieces. However, although twenty breaches of the Code were ruled many of the matters overlapped. The two leavepieces were part of the same (launch) campaign for Flutiform and so in that regard the breaches had occurred in parallel; Napp had not repeated breaches of the Code from one campaign to another and over a period of time.

The Appeal Board was further concerned that the leavepieces might have encouraged the use of Flutiform in patients for whom it was not indicated and also the inappropriate switching of patients from Seretide to Flutiform on the basis of, *inter alia*, cost. The Appeal Board considered, however, that prescribers would be well aware that asthma devices were not like-for-like and so direct substitution would be unlikely. In the Appeal Board's view when asthmatics were changed from one medicine to another, processes were established to ensure that patient safety was protected and prescribers would be reluctant to switch well-controlled patients.

The Appeal Board noted that the Panel had ruled a breach of Clause 9.1 as high standards had not been maintained. The Appeal Board noted its concerns about the breaches of the Code and the possible, theoretical adverse consequences of some of the claims on patient safety but considered that, on balance, the circumstances did not warrant a breach of Clause 2 and it upheld the Panel's ruling of no breach of that clause. The appeal was thus unsuccessful.

Complaint received	**19 December 2012**
Case completed	**17 July 2013**