ANONYMOUS, NON CONTACTABLE v GLAXOSMITHKLINE

Promotion of Relvar

An anonymous, non contactable complainant who described him/herself as a prescriber complained that GlaxoSmithKline UK was trying to hide important safety information in relation to promotion of Relvar Ellipta (fluticasone furoate/ vilanterol inhalational powder).

The complainant highlighted a claim in an email that 'Relvar is generally well-tolerated in COPD. The risk of pneumonia in COPD patients with Relvar 92/22mcg is similar to that reported within the Summary of Product Characteristics of other commonly used ICS/LABAs' [inhaled corticosteroid and long-acting ß$_2$ adrenoreceptor agonists].

The complainant stated that reading the email led him/her to believe that pneumonia was a side-effect associated with COPD only as highlighted on the second page; there was no mention of pneumonia with regard to asthma. The complainant stated that he/she did not think too much about it at the time as pneumonia was associated with the use of ICS/LABA in COPD patients. There was not the same association with asthma so it seemed to be as expected. However, on reading the Drug and Therapeutics Bulletin (DTB) review, the complainant was surprised to note that pneumonia had been reported in asthma patients on Relvar and GlaxoSmithKline had been required by the regulators to study this further.

The complainant looked at the GlaxoSmithKline website and noted that the information was similar to that received in the email. A number of screen shots were provided. The website only discussed pneumonia in relation to COPD with no mention of asthma.

The complainant noted that pneumonia was mentioned in the SPC with regard to both COPD and asthma. The complainant stated that hidden in the text was the important information that the incidence of pneumonia in patients with asthma was common at the higher dose. The incidence of pneumonia in patients with asthma who took fluticasone furoate/vilanterol 184/22mcg was numerically higher compared with those who took fluticasone furoate/vilanterol 92/22mcg or placebo (see section 4.8). No risk factors were identified.

The complainant noted that the incidence of pneumonia was common in asthma patients taking the higher dose. The complainant alleged that for GlaxoSmithKline to discuss pneumonia only in relation to COPD in its advertisements, which was expected for that type of inhaler, while omitting that it was commonly experienced in asthma patients which was an unexpected side-effect, was totally unacceptable and a risk to patient safety.

The complainant referred to GlaxoSmithKline's statement that the incidence of pneumonia in COPD patients was similar to that of other commonly used ICS/LABAs quoting the SPCs for Seretide and Symbicort. The complainant noted that GlaxoSmithKline had not included Fostair in the comparison which, although only recently licensed for COPD, was commonly used to treat the condition. Fostair information stated that pneumonia was uncommon and the complainant alleged that this was another example of important safety information being hidden and not included in GlaxoSmithKline materials.

The detailed response from GlaxoSmithKline is given below.

The Panel noted the complainant was anonymous and non-contactable. As stated in the introduction to the Constitution and Procedure such complaints were accepted and like all complaints, judged on the evidence provided by both parties. Complainants had the burden of proving their complaint on the balance of probabilities.

The Panel noted that the DTB section was headed 'Unwanted effects' and stated 'Although pneumonia is more common in patients with chronic obstructive pulmonary disease (COPD) it has been reported in patients receiving fluticasone/vilanterol for asthma. The company is required to conduct a further study into the risk of pneumonia as an obligatory post-authorisation measure'.

The Panel noted the complainant's concern that GlaxoSmithKline was trying to hide important safety information on pneumonia as a side effect associated with using Relvar to treat asthma. The email provided by the complainant specifically highlighted pneumonia as a side effect associated with COPD but not asthma. GlaxoSmithKline stated that the clinical and management considerations for pneumonia in COPD was different to that in asthma. COPD patients were at higher risk of developing CAP than those in the general population and those with asthma. COPD patients with pneumonia had worse clinical outcomes compared with pneumonia patients without COPD in terms of pneumonia severity, intensive care admissions, and mortality (Restrepo *et al*, 2006). The rates of pneumonia seen in COPD were significantly higher than the rates seen in asthma patients, including, importantly, rates of serious and severe events. This was expected based on the different disease profiles and the differing prognoses for pneumonia in the two conditions. That pneumonia was a more important clinical condition in COPD compared with asthma was highlighted by UK and international guidelines. The Panel also noted the Cochrane Review report

on inhaled steroids and risk of pneumonia in COPD, Kew *et al* 2014, concluded that budesonide and fluticasone delivered as monotherapy or in combination with a LABA were associated with increased risk of a serious adverse pneumonia event but neither significantly effected mortality compared with controls. The safety concerns highlighted in the review should be balanced with recent cohort data and established evidence of efficacy regarding exacerbations and quality of life.

The Panel noted the submission from GlaxoSmithKline that overall, the incidence of pneumonia in asthma was low (≤1.1%) in all treatment groups. The highest incidence of 1.1% for Revlar 200/25 corresponded to five patients. Nonetheless, the Panel noted GlaxoSmithKline's submission that pneumonia was correctly described as a common adverse event in the SPC. The Panel noted the concerns raised about pneumonia in the Discussion of Clinical Safety section of the EMA Revlar assessment report. The regulators required GlaxoSmithKline to continue to gather information about the risk associated with Relvar (a combination of new chemical entities) in both asthma and COPD compared with other licensed ICS/LABAs.

The Panel did not consider that mentioning pneumonia in relation to COPD patients in the email meant that it did not have to be considered in asthma patients. The Panel noted GlaxoSmithKline's comments about the importance of pneumonia in COPD compared to asthma. On balance, the Panel considered that it was therefore not unreasonable to mention pneumonia in relation to COPD alone. No breaches of the Code were ruled.

The Panel noted the complainant was concerned that GlaxoSmithKline had not compared Relvar to Fostair, which was recently licensed for COPD. The Panel noted the claim in the email stated, 'Relvar is generally well tolerated in COPD. The risk of pneumonia in COPD patients with Relvar 92/22mcg is similar to that reported within the Summary of Product Characteristics of other commonly used ICS/LABAs'. GlaxoSmithKline stated that the most commonly prescribed ICS/LABAs in the UK for COPD were Seretide and Symbicort (June 2013 – June 2014). The FORWARD study (Wedzicha *et al*, 2014), showed that pneumonia occurred in 3.8% of Fostair patients vs 1.8% in the formoterol (LABA alone) group and concluded 'The [Fostair] treatment arm was also associated with a higher incidence of pneumonia. This is in line with recent studies showing a 2-3 fold excess of pneumonia in the ICS/LABA treatment arms of studies compared to the corresponding monotherapy.' Calverley 2010 reported pneumonia in 2.1% of Fostair patients, 2.9% of Symbicort patients and 0.4% in the formoterol group and concluded: 'The rate of reported pneumonia was similar to that reported in placebo controlled trials using budesonide.' GlaxoSmithKline submitted that the association of pneumonia with ICS in COPD was regarded as a class effect and therefore similar risks of pneumonia could be expected with Relvar, Seretide, Symbicort and Fostair.

The Panel noted the complainant had not provided any information to support his/her view that Fostair was commonly used to treat COPD. Fostair 100/6 was indicated for symptomatic treatment of patients with severe COPD (FEVI <50% predicted normal) and a history of repeated exacerbations. Pneumonia was listed as an uncommon (≥1/1000 and <1/100) undesirable effect (derived from clinical trials in asthmatic and COPD patients). The SPC included an asterisk next to pneumonia and the explanation 'one related non serious case of pneumonia was reported by one patient treated with Fostair in a pivotal clinical trial in COPD patients'.

The Panel noted the complaint was received in August. The email referred to the SMC decision in April 2014 and that AWMSG would be discussing, Relvar in asthma in July 2014. The Panel noted the data provided by GlaxoSmithKline showed that Fostair was not commonly prescribed for COPD around that time. There was a difference in indications. Fostair was only licensed for severe COPD. Although there appeared to be a difference between Fostair and Relvar with regard to whether pneumonia in COPD was common or uncommon as an undesirable effect in the SPCs, the data submitted by GlaxoSmithKline appeared to support similarities between the products. On the evidence before it the Panel did not consider the comparison was misleading and at the time the email was sent GlaxoSmithKline had not 'cherry picked' the information as alleged. No breaches of the Code were ruled.

The Panel then considered the allegation about the GlaxoSmithKline website and the screen shot provided by the complainant who had highlighted a section of the website for Budget Holders where three options were provided: 'Making a formulary application in asthma', 'Making a formulary application in COPD' and 'Need a quick reference guide for a formulary application for Relvar Ellipta'. The screen shots provided by the complainant appeared to come from the section 'Need a quick reference guide for a formulary application for Relvar Ellipta'.

The Panel noted its comments and rulings above. Bearing in mind that detailed information was provided about pneumonia in asthma in the section 'Making a formulary application in asthma' (as well as pneumonia and COPD in the section 'Making a formulary application in COPD') and each section included links to the prescribing information and SPCs, the Panel considered that information on pneumonia as a side-effect in patients with asthma was available. The Panel did not consider that the section of the website for budget holders 'Need a quick reference guide for a formulary application for Revlar Ellipta' was misleading about the incidence of pneumonia in asthma nor did it fail to reflect the available evidence as alleged. No breaches of the Code were ruled.

The Panel did not consider that GlaxoSmithKline had failed to maintain high standards or had brought discredit on the pharmaceutical industry. Thus the Panel ruled no breach including of Clause 2.

An anonymous, non contactable complainant who described him/herself as a prescriber complained about the promotion of Relvar Ellipta (fluticasone furoate/vilanterol inhalational powder) by GlaxoSmithKline UK Limited and in particular an email (ref UK/FFT/0332/14).

Relvar Ellipta 92/22mcg was indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting $beta_2$-agonist and inhaled corticosteroid) was appropriate. The summary of product characteristics (SPC) referred in this regard to patients not adequately controlled with inhaled corticosteroids and as needed inhaled short-acting $beta_2$-agonists. Relvar Ellipta 92/22mcg was also indicated for the symptomatic treatment of adults with chronic obstructive pulmonary disease (COPD) with a FEV1 <70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.

Relvar Ellipta 184/22mcg was indicated similarly for asthma, it was not indicated for COPD.

The email was sent to subscribers of Nursing in Practice who GlaxoSmithKline submitted had agreed to receive promotional materials from pharmaceutical companies. There were differences between the email supplied by GlaxoSmithKline and the screen shots of the email provided by the complainant which appeared to be incomplete. The GlaxoSmithKline copy was headed RELVAR and had four distinct sections including: Scottish Medicines Consortium (SMC) issues guidance for Relvar in asthma and All Wales Medicines Strategy Group (AWSMG) issues guidance for Relvar in COPD. Both of these sections included the executive summary of the advice and a link to the website where full guidance could be accessed. The third section of the email discussed Relvar Ellipta and its use in asthma and COPD including the indications. The final section consisted of a list of references, the prescribing information and adverse event reporting requirements. The heading and introduction to the SMC section and part of the executive summary to the AWSMG section was missing from the copy supplied by the complainant.

The complainant highlighted a claim, within the Relvar Ellipta summary section, 'Relvar is generally well-tolerated in COPD. The risk of pneumonia in COPD patients with Relvar 92/22mcg is similar to that reported within the Summary of Product Characteristics of other commonly used ICS/LABAs' [inhaled corticosteroid and long-acting $ß_2$ adrenoreceptor agonists].

COMPLAINT

The complainant was concerned that GlaxoSmithKline was trying to hide important safety information having seen its advertising in a number of places including the internet, on stands at conferences, in emails and in letters.

The complainant stated that he/she was encouraged to contact the PMCPA after receiving an email regarding Relvar and reading a Drug and Therapeutics Bulletin (DTB) review. The complainant stated that reading the email led him/her to believe that pneumonia was a side-effect associated with COPD only as highlighted on the second page; there was no mention of pneumonia with regard to asthma. The complainant stated that he/she did not think too much about it at the time as pneumonia was associated with the use of ICS/LABA in COPD patients. There was not the same association with asthma so it seemed to be as expected. However, on reading the DTB review, the complainant was surprised to note that pneumonia had been reported in asthma patients on Relvar and GlaxoSmithKline had been required by the regulators to study this further.

The complainant looked at the GlaxoSmithKline website and noted that the information was similar to that received in the email. A number of screen shots were provided. The website only discussed pneumonia in relation to COPD with no mention of asthma.

The complainant then looked at the Relvar SPC and noted that pneumonia was mentioned with regard to both COPD and asthma. The complainant stated that hidden in the text was the important information that the incidence of pneumonia in patients with asthma was common at the higher dose. The incidence of pneumonia in patients with asthma who took fluticasone furoate/vilanterol 184/22mcg was numerically higher compared with those who took fluticasone furoate/vilanterol 92/22mcg or placebo (see section 4.8). No risk factors were identified.

The complainant noted that the incidence of pneumonia was common in asthma patients taking the higher dose. The complainant alleged that for GlaxoSmithKline to discuss pneumonia only in relation to COPD in its advertisements, which was expected for that type of inhaler, while omitting that it was commonly experienced in asthma patients which was an unexpected side-effect, was totally unacceptable and a risk to patient safety. The complainant stated that as a prescriber that was the sort of information he/she wanted to know and that GlaxoSmithKline would want to hide.

The complainant further stated that he/she would like to address the fact that GlaxoSmithKline stated that the incidence of pneumonia in COPD patients was similar to that of other commonly used ICS/LABAs quoting the SPCs for Seretide and Symbicort. The complainant noted that it was true that both of these products had pneumonia commonly reported but GlaxoSmithKline had not included Fostair in the comparison which, although only recently licensed for COPD, was commonly used to treat the condition. Fostair information stated that pneumonia was uncommon and the complainant alleged that this was another example of GlaxoSmithKline cherry-picking the information it used. Important safety information was being hidden and not included in GlaxoSmithKline materials.

The complainant requested that the matter be taken up with GlaxoSmithKline as he/she alleged that it

was dishonest, potentially put patient safety at risk and hid information that prescribers needed to know. The complainant stated that if there were several other inhalers he/she could prescribe, why would he/she give the one that could cause pneumonia to his/her asthma patients. The complainant thought that GlaxoSmithKline should have to send a corrective notification to prescribers as a matter of urgency.

When writing to GlaxoSmithKline, the Authority asked it to respond in relation to Clauses 7.2, 7.3, 7.4, 7.9, 7.10, 9.1 and 2 of the Code.

RESPONSE

GlaxoSmithKline explained that Relvar Ellipta was a new inhaled ICS/LABA combination product, which was licensed in the UK for asthma and COPD. It had been generally available since January 2014.

Asthma indication

> The regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta$_2$-agonist and inhaled corticosteroid) is appropriate:
>
> - patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta$_2$-agonists.

COPD indication

> The symptomatic treatment of adults with COPD with a FEV1 <70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.

Two doses were licensed in asthma, 92/22mcg and 184/22mcg; only the 92/22mcg dose was licensed in COPD. The 92/22mcg and 184/22mcg values represented the delivered doses (dose leaving the mouthpiece); this corresponded to pre-dispensed doses of 100/25mcg and 200/25mcg respectively.

Asthma

Relvar and pneumonia in asthma

GlaxoSmithKline submitted that although pneumonia was more common and seen to be a greater clinical challenge in COPD, it was also reported as a known adverse event associated with ICS/LABA use in asthma. This important point was highlighted clearly within the European Medicines Agency (EMA) Product Assessment Report (EPAR) for Relvar Ellipta (September 2013):

> 'In the asthma programme, the incidence of Community Acquired Pneumonia (CAP) for [fluticasone furoate] containing (ie [fluticasone fuorate and fluticasone fuorate/vilanterol]) groups was within the same range of incidences seen with other ICS.'

Overall, the incidence of pneumonia was low (≤1.1%) in all treatment groups with the 95% confidence intervals for both the incidence and the exposure rate overlapping across treatment groups, including placebo. The data was based on a review of 17 asthma studies from the Relvar clinical development programme, which included 7,199 patients and details from Ellipta EPAR 2013 and GlaxoSmithKline data on file were provided.

GlaxoSmithKline submitted that the data showed that the incidence of pneumonia ranged from 0.6% in the fluticasone 100mcg containing arms to 0.5-1.1% in the fluticasone 200mcg containing arms; this corresponded to event rates/1,000 treatment years of between 8.4 and 20.9 respectively. Furthermore, in absolute terms, this also represented a low number of individual patients; the highest incidence of 1.1% for Relvar 200/25 corresponded to 5 individual patients. Indeed, if pneumonia had only occurred in 4 patients the frequency would have been 0.8% ie uncommon. The incidence in the placebo arm was 0.2% with an event rate/1,000 treatment years of 9.6. GlaxoSmithKline noted that placebo was only included in studies of 6 months' duration compared with a maximum duration of 52–76 weeks for studies of Relvar 200/25mcg and 100/25mcg.

Overall, the incidence of serious pneumonia was low and similar across groups including placebo (0.1-0.3%; 2.8-5.2 events/1,000 treatment years). This was also the case for severe pneumonia (0.0-0.4%; 0-7.4 events/1,000 treatment years). Again absolute numbers of patients for both these parameters were very low (0-5 patients). Serious pneumonia events were those that required hospitalisation, whilst the definition of severe pneumonia was based on the investigator's adjudication on whether an episode was mild, moderate or severe.

Within the Relvar asthma clinical development programme there was one study which directly compared Relvar with a marketed ICS/LABA, Seretide (fluticasone propionate/salmeterol). Within this 24 week study, there were no events of pneumonia in the Relvar arm compared with 2 in the Seretide group including 1 serious pneumonia event. No severe pneumonia events were reported in either treatment group (Relvar Ellipta EPAR 2013).

GlaxoSmithKline stated that as there was only one direct head-to-head study vs a licensed ICS/LABA, of only 24 weeks' duration, it was considered appropriate during the regulatory review process to also submit indirect comparisons with pre-existing studies undertaken for Seretide, an established and commonly used ICS/LABA in the UK. This analysis showed that the rates of pneumonia seen were within the same range as that seen with other ICS/LABAs (Relvar Ellipta EPAR 2013). GlaxoSmithKline noted that the highest incidence seen in the Relvar 200/25mcg group (18.4 events/1,000 treatment years) was very similar to the highest incidence of 19.7 events/1,000 treatment years seen in the Seretide 250/50mcg bd group in the integration of the Seretide studies data from the EPAR was provided. The EMA reached the same conclusion as reported in the Relvar EPAR.

GlaxoSmithKline also provided data for budesonide (BUD) which was the steroid contained in Symbicort, another commonly used ICS/LABA in asthma.

GlaxoSmithKline submitted that here too the percentage of subjects who developed pneumonia was 0.8% and 1.0% for doses of 400mcg and 800mcg respectively, which equated to an event rate/1,000 treatment years of 21.8 and 33.9. However, these values needed to be considered in light of the relatively small number of patients who had events.

O'Byrne *et al* (2011) undertook a retrospective analysis which evaluated studies in asthmatics (n=48,489) which included the use of the inhaled steroids budesonide and fluticasone, as well as placebo. The occurrence of pneumonia in this analysis ranged from 0.5% (rate 10 events/1,000 patient years) and 1.2% (rate 19.3 events/1,000 patient years), with the higher value in the placebo arms. These values once again demonstrated that pneumonia was seen with asthmatic patients who were enrolled in clinical trials and that, as seen with Relvar, these rates were generally low.

Lastly, GlaxoSmithKline noted that prospective studies from the UK, Finland and North America had reported an incidence of community acquired pneumonia diagnosed in the general population of between 5 and 11 per thousand adult population, ie 0.5-1.1% (British Thoracic Society Guidelines for the management of community acquired pneumonia in adults: update 2009).

Therefore, from the above it could be seen that pneumonia was a potential side effect associated with the use of all Relvar doses in patients with asthma. Although classed correctly as a common adverse event, ie with an occurrence of ≥1.0 – <10%, the incidence of pneumonia was low (0.6%-1.1%) and most importantly the rates were similar to those seen with other established, licensed ICS/LABAs which were commonly used for asthma in the UK.

The low numbers of pneumonia events which occurred in the Relvar asthma development programme, coupled with the limitations inherent in indirect analyses meant that the regulators required GlaxoSmithKline to continue to gather ongoing information to further characterise the risk associated with Relvar (a combination of new chemical entities) in asthma compared with other licensed ICS/LABAs. This would be undertaken through continual, proactive pharmacovigilance activities as well as the assessment of pneumonia in the Salford Lung Study; a real world effectiveness study which compared the use of Relvar, in routine clinical practice, with existing therapy.

COPD

Pneumonia in COPD

GlaxoSmithKline submitted that the clinical picture and management considerations for pneumonia in COPD patients was different to that in asthma. In early COPD, the damage to the innate immune system promoted colonisation and an increase in risk of respiratory tract infections (Vestbo *et al*, 2006). COPD patients were at higher risk of developing community acquired pneumonia than those in the general population and those with asthma. A recent, UK, population-based, retrospective, database study of 40,414 COPD patients estimated the incidence of community acquired pneumonia to be 22.4 episodes/1,000 person years (Mullerova *et al*, 2012). Higher background rates had been reported in the placebo/non-ICS arms of clinical trial populations (52 events/1,000 treatment years; TORCH study, Crim *et al*, 2009). COPD patients with pneumonia had also been shown to have worse clinical outcomes compared with similarly aged pneumonia patients without COPD in terms of pneumonia severity, intensive care admissions, and mortality (Restrepo *et al*, 2006).

Increased pneumonia risk with inhaled corticosteroids – class effect

GlaxoSmithKline submitted that there was strong evidence from several independent meta-analyses that the risk of pneumonia in COPD patients was increased with the use of inhaled corticosteroids (ICS) when compared with non-ICS control arms. This was a well established class effect (Kew *et al*, 2014; Symbicort/Seretide/Relvar SPCs). Evidence that the risk of pneumonia in COPD was comparable across all ICS/LABAs, including Relvar, was published in an independent Cochrane meta-analysis (Kew *et al*, 2014). This showed no significant difference in the risk of serious pneumonia leading to hospitalisation for fluticasone furoate, fluticasone propionate or budesonide containing treatments compared with no-ICS controls. A difference in non-serious pneumonias was observed as a consequence of non-standardised pneumonia definitions in the different studies included in the meta-analysis, leading to substantial heterogeneity in the treatment effects, and reduced confidence in the findings.

Additionally, following the review of the available evidence, the 2010 National Institute of Health and Care Excellence (NICE) guideline on COPD concluded that:

> 'meta-analysis showed a statistically-significantly greater incidence of pneumonia in the LABA+ICS arm compared with the LABA arm (where the studies were of greater than six months' duration). The Guidance Development Group (GDG) noted that, although there was a difference, the absolute risk of pneumonia was low. The GDG also considered whether this was a class effect or related to a specific steroid molecule, but the published evidence available at the time of guideline development did not allow them to reach a conclusion on this point.'

Relvar and pneumonia in COPD

GlaxoSmithKline stated that an extremely robust approach to the monitoring and reporting of pneumonia was adopted in the Relvar clinical development programme to avoid any potential under reporting of pneumonias: pneumonia was pre-defined as an adverse event of special interest and investigators were provided with a list of specific criteria which could indicate a diagnosis of pneumonia, to standardise the diagnosis. Finally, in the 52 week exacerbation studies, which included patients at higher risk of pneumonia,

chest radiographs were performed at baseline and within 48 hours of any suspected pneumonia or exacerbation.

In the pooled analysis of these 2 one year studies, pneumonia was noted in 6.3% of patients who received Relvar 92/22mcg, compared with 3.3% of patients receiving only vilanterol 22mcg, ie LABA alone (Dransfield *et al*, 2013). The number of pneumonia events/1,000 patient years was 85.7 for the Relvar 92/22mcg arm and 42.3 in the vilanterol 22mcg arm. For severe pneumonia the corresponding number of events/1,000 patient years were 35.5 and 7.6 for Relvar 92/22mcg and vilanterol 22mcg respectively, while for serious pneumonia the corresponding events/1,000 patient years were 42.9 with Relvar 92/22mcg and 12.1 with vilanterol 22mcg (Relvar Ellipta SPC, 2013).

GlaxoSmithKline stated that the rate of pneumonia observed with Relvar 92/22mcg was consistent with that observed for the other ICS/LABA preparations licensed in COPD. The absolute rates of pneumonia would vary from study to study due to differences in study design, baseline patient characteristics and definitions of pneumonia, however, what was expected was that there was a difference (generally 2 fold) between the rates seen in the ICS containing arms vs those seen in the non ICS containing arm. From the TORCH study the estimated 3 year probability of having pneumonia was 19.6% for patients on Seretide 500/50mcg (n=1,546) compared with a rate of 12.3% observed for placebo (n=1,554) (Calverley *et al*, 2007). The Symbicort SPC (2013) stated that since Symbicort contained budesonide and formoterol, the same pattern of undesirable effects as reported for these substances might occur. With respect to pneumonia, the Symbicort SPC stated:

> 'In a 3-year clinical trial with budesonide in COPD, skin bruises and pneumonia occurred at a frequency of 10% and 6%, respectively, compared with 4% and 3% in the placebo group ($p<0.001$ and $p<0.01$, respectively).'

Fostair and pneumonia in COPD patients

GlaxoSmithKline stated that the data reviewed for the 2014 Kew Cochrane review the NICE 2010 COPD guidance did not include studies for Fostair, as this only received a COPD licence in 2014. Fostair (beclometasone/formoterol) contained a different steroid component, beclometasone, to that within Seretide, Symbicort or Relvar. However, as highlighted above the evidence indicated that the increased incidence of pneumonia associated with ICS use was a class effect with no difference seen between the different steroid molecules.

The Fostair COPD clinical development programme included two 48 week studies. In the FORWARD study (Wedzicha *et al*, 2014), pneumonia occurred in 3.8% in the Fostair group vs 1.8% in the formoterol (LABA alone) group. The authors of the study concluded:

> 'The [Fostair] treatment arm was also associated with a higher incidence of pneumonia. This is in line with recent studies showing a 2-3 fold excess of pneumonia in the ICS/LABA treatment arms of studies compared to the corresponding monotherapy.'

Within the other study (Calverley 2010), pneumonia was reported in 2.1% of Fostair patients, 2.9% of Symbicort patients and 0.4% in the formoterol group. The authors concluded:

> 'The rate of reported pneumonia was similar to that reported in placebo controlled trials using budesonide.'

Therefore, as could be seen from the above, GlaxoSmithKline submitted that the association of pneumonia with ICS in COPD was regarded as a class effect and therefore similar risks of pneumonia could be expected with Relvar, Seretide, Symbicort and Fostair.

Clinical importance of pneumonia in COPD and asthma

GlaxoSmithKline noted that all the pneumonia rates in COPD discussed above were significantly higher than the rates seen in asthma patients, including, importantly, rates of serious and severe events. As discussed above this was expected based on the different clinical and pathophysiological profiles of the diseases involved and the differing prognoses for pneumonia in the two conditions. That pneumonia was a more important clinical condition in COPD compared with asthma was highlighted by UK and international guidelines. In NICE and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD guidelines, pneumonia was discussed as an important risk for COPD patients, with pneumococcal vaccination being recommended for all patients. BTS/Scottish Intercollegiate Guidelines Network (SIGN) and Global Initiative for Asthma (GINA) asthma guidelines did not specifically discuss pneumonia.

Provision of safety information within promotional material

GlaxoSmithKline referred to Clauses 7.2, 7.3, 7.4, 7.9 and 7.10 and the Medicines and Healthcare Products Regulatory Agency (MHRA) Blue Guide, 2012. This stated that:

> 'Claims that a medicine is generally well tolerated, including claims relating to the overall incidence of side effects versus placebo in clinical trials, may be acceptable if supported by evidence, provided a misleading impression is not given.'
> 'Care should be taken to ensure that prescribers are not misled by promotional claims in advertising which suggests that a particular product is safer than an alternative medicine unless this is supported by evidence.'

GlaxoSmithKline submitted that the amount of safety information contained in a promotional item (in addition to the prescribing information) varied depending on the item in question. A one page journal advertisement or email would contain less information than a twenty page detail aid. The

amount was also in part determined by how much efficacy information was included, such that any efficacy claims could be appropriately balanced with consideration of the safety profile. Also, certain adverse events which were of particular importance for clinicians and patients, based on factors such as their frequency rate and/or the potential clinical consequences associated with them, should be highlighted in all materials where efficacy data was shared. These factors were taken into consideration when deciding what safety information to include in Relvar promotional materials.

Response to allegations

1 Pneumonia is not an adverse effect associated with ICS/LABAs in asthma; it is only seen in COPD. Relvar Ellipta has a unique safety signal amongst ICS/LABAs in asthma, as pneumonia is a common adverse event in patients taking the higher dose

The complainant stated that there was not an association between ICS/LABA usage in asthma and pneumonia and thus for pneumonia to be an adverse effect associated with the use of Relvar in asthma was unexpected and a unique safety signal. GlaxoSmithKline stated that this assertion was not correct. As discussed above, pneumonia was a known side effect associated with ICS/LABA usage in asthma. The rates of pneumonia seen in asthma patients in the Relvar clinical trial programme were low (0.6-1.1%) and importantly (as concluded by the EMA) consistent with those seen with other established and commonly used ICS/LABAs in asthma, such as Seretide.

2 Promotional email with no information on pneumonia in asthma (UK/FFT/0332/14)

GlaxoSmithKline noted that the first item highlighted by the complainant was a promotional email sent to subscribers of Nursing in Practice who had agreed to receive promotional material from pharmaceutical companies. The first part of the email highlighted that the Scottish Medicines Consortium (SMC) in asthma and the All Wales Medicines Strategy Group (AWMSG) in COPD had issued advice for Relvar Ellipta. The executive summary from the SMC and AWMSG guidance was quoted in full in accordance with their policies. The second half of the email contained the following promotional claims for Relvar as well as the indications in asthma and COPD; GlaxoSmithKline noted that no data was presented.

> 'The first ICS/LABA combination to deliver continuous 24 hour efficacy in a practical once daily dose.'
>
> 'Delivered in a straightforward device.'
>
> 'That offers value to the NHS.'

A limited amount of information was provided here, however in order to present fair balance, a succinct summary of the relevant safety information was also provided. The safety profile for Relvar in asthma, as concluded in the EPAR, was consistent with other ICS/LABAs with regard to the nature, frequency and severity of the adverse effects seen, including, *inter alia*, pneumonia; as a result it could be considered to be generally well tolerated. The use of such a statement was in line with the advice within the MHRA Blue Guide. ICS/LABAs were commonly used asthma treatments and were a class of medicine with which prescribers in primary and secondary care had several years' experience. As highlighted above, pneumonia, due to frequency and clinical characteristics, was not as major a concern in asthma as it was in COPD.

Of all the adverse events associated with ICS/LABAs in COPD it was clear that there was increased clinical importance associated with the potential adverse event of pneumonia. It was important that health professionals should be told that the risk of pneumonia associated with Relvar was similar in magnitude to that associated with other ICS/LABAs. Therefore, an additional statement about pneumonia and COPD was included.

In line with Clause 4.1, prescribing information formed part of this email and this listed all the adverse events, including pneumonia, which might occur in patients with asthma and COPD.

Lastly, the MHRA pre-vetted Relvar promotional material before launch, in line with its commitment to vet advertising for all new active substances. As part of this process, material with a similar balance of efficacy and safety messages was reviewed by the MHRA and no objections regarding these safety statements were raised.

3 Prescribing information on promotional email UK/FFT/0332/14

GlaxoSmithKline noted the complainant's concern about the information contained in the prescribing information. He/she stated that GlaxoSmithKline had omitted the fact that pneumonia was an adverse effect in asthma identifying the text contained within the 'Precautions' section. Clause 4.2 of the Code included:

> 'A succinct statement of common adverse reactions likely to be encountered in clinical practice, serious adverse reactions and precautions and contra-indications relevant to the indications in the advertisement, giving, in an abbreviated form, the substance of the relevant information in the summary of product characteristics, together with a statement that prescribers should consult the summary of product characteristics in relation to other adverse reactions.'

The Relvar prescribing information (UK/RESP/0209a/13), which was on all promotional material for asthma, contained pneumonia as a common side effect, thus informing prescribers that, as seen with other ICS/LABAs, there was a risk of pneumonia associated with the use of Relvar in asthma. If this risk had been associated with COPD only it would not appear in prescribing information

for asthma as it would not be relevant to the indication in the advertisement. The Relvar SPC stated the following:

> 'With the exception of pneumonia and fractures, the safety profile was similar in patients with asthma and COPD. During clinical studies, pneumonia and fractures were more frequently commonly observed in patients with COPD.'

This was deliberately omitted from the prescribing information, as in isolation clinicians might misinterpret this as suggesting that pneumonia only occurred in COPD.

Clause 4.2 required serious adverse events and precautions and contraindications to be succinctly summarised. The precautions section of the Relvar SPC contained a section entitled 'Pneumonia in patients with COPD'. Due to the serious nature of pneumonia in COPD, a precaution about COPD and pneumonia and identified risk factors was included in the prescribing information. The last paragraph of the SPC under this specific heading stated:

> 'The incidence of pneumonia in patients with asthma was common at the higher dose. The incidence of pneumonia in patients with asthma taking fluticasone furoate/vilanterol 184/22 micrograms was numerically higher compared with those receiving fluticasone furoate/vilanterol 92/22 micrograms or placebo (see section 4.8). No risk factors were identified.'

The key information here was that pneumonia was common in asthma patients, however this information was already included in the adverse event listings within the prescribing information and thus further information was not provided in the precautions section. To include the wording 'The incidence of pneumonia in patients with asthma taking fluticasone furoate/vilanterol 184/22mcg was numerically higher compared with those receiving fluticasone furoate/vilanterol 92/22mcg or placebo' within the prescribing information would not be appropriate as it would require qualification with the actual numbers involved so that clinicians would know that the incidence rates discussed were 0.6 vs 1.1%. The provision of such detail within the prescribing information would not be appropriate for a succinct summary of adverse events. Using the same rationale specific rates of pneumonia in COPD were also not included in the prescribing information. Finally, as required by the Code, the prescribing information advised prescribers to consult the SPC before prescribing, as the detail contained within the SPC could never be captured by the prescribing information alone.

The prescribing information highlighted above had also undergone MHRA pre-vetting; no objections were raised by the MHRA.

4 Promotional material on GSK website [UK/FFT/0019e/13(2)]

GlaxoSmithKline noted that the complainant also highlighted information for Relvar available on health.gsk. This was a GlaxoSmithKline website and the sections discussed were clearly identified as being intended for health professionals. Within the Relvar pages of the website there was a number of sections, including one dedicated to safety. The complainant highlighted information contained within the section entitled 'Budget Holders'. Within this section there were three options the viewer could select including 'Making a formulary application in asthma – Use the Relvar Ellipta asthma pack to support your application'. This section provided a detailed overview of the efficacy and safety data in asthma including an adverse events table which listed pneumonia as the first common adverse event within the organ class of 'Infection and infestations'. Below this table a section entitled 'Pneumonia' stated the following:

> 'In clinical trials of asthma patients the incidence of pneumonia seen with Relvar 92/22mcg was similar to that of placebo. There was a higher incidence of pneumonia with the 184/22mcg compared to the 92/22mcg strength. Few of the pneumonia events lead to hospitalisation with either strength. The number of pneumonia events per 1,000 patient years was 18.4 for fluticasone furoate/vilanterol (Relvar) 184/22mcg vs 9.6 for fluticasone furoate/vilanterol (Relvar) 92/22mcg and 8.0 in the placebo group (<1% overall).'

GlaxoSmithKline submitted that the existence of this information on its website which could be accessed by any UK health professional clearly demonstrated that the company had not hidden information which stated that pneumonia could occur in asthma patients treated with Relvar.

GlaxoSmithKline noted that the complainant, however, had not highlighted this page of the website, but had instead chosen a page within the section for budget holders' 'Need a quick reference guide for a formulary application for Relvar Ellipta?'. Within this page a less detailed, top-line summary was provided of the indications and the key efficacy conclusions. As a result, less safety information was provided with it being stated that Relvar was generally well tolerated in asthma and COPD. Based on the same rationale highlighted above (clinical importance of pneumonia in COPD), further detail was, however, provided for pneumonia in COPD including incidence rates. A link to the prescribing information and SPC was also provided on this page. GlaxoSmithKline noted that this page sat within the overall Relvar website which contained easily accessible sections dedicated to more detailed safety.

5 Use of the statement 'The risk of pneumonia in COPD patients with Relvar 92/22mcg is similar to that reported within the summary of product characteristics of other commonly used ICS/LABAs'

GlaxoSmithKline submitted that UK prescription data (Cegedim Longitudinal Patient Database; July 2013 – June 2014) showed that the most commonly prescribed ICS/LABAs in the UK for COPD were Seretide and Symbicort. Details were provided.

In addition, both of these established medicines had been available for use in the UK for COPD for a number of years and as such clinicians would be familiar with prescribing them; Fostair received a marketing authorization in COPD in 2014. Therefore, it was important that health professionals were aware that the risk of pneumonia with a new medicine such as Relvar was similar to that which they knew and were used to dealing with for Seretide and Symbicort.

As discussed above, Fostair was also associated with pneumonia and, as would be expected for a class effect, the risk of pneumonia was no different to Relvar, Seretide or Symbicort.

Conclusion

GlaxoSmithKline concluded that:

- Relvar did not have a unique pneumonia safety signal amongst ICS/LABAs used in asthma. The incidence of pneumonia in the Relvar asthma clinical trial programme was low and consistent with other licensed ICS/LABAs.

- The prescribing information for all Relvar asthma materials stated that pneumonia was a common adverse event. Additionally, all Relvar asthma material which contained a significant amount of efficacy data had included in the safety section, as a minimum, a table which highlighted that pneumonia was a common adverse event.

- The increased risk of pneumonia seen in COPD patients treated with ICS/LABAs was a class effect. A similar risk was reported in the clinical trials of Relvar, Seretide, Symbicort and Fostair.

GlaxoSmithKline strongly believed that its Relvar asthma and COPD promotional materials were accurate, balanced, fair, objective and that a clear overview of the safety information had been provided and that this was not misleading, and could be substantiated by data and clinical experience.

The discussion of pneumonia risk in COPD amongst ICS/LABAs was an appropriate comparison of an important, relevant and representative feature. A balanced, objective and up-to-date evaluation of all the evidence had been undertaken and reflected in a manner which could be substantiated.

As a result, Relvar promotional materials encouraged the rational use of the medicine in patients with asthma and COPD.

GlaxoSmithKline therefore refuted any breach of Clauses 7.2, 7.3, 7.4, 7.9 and 7.10. In the absence of these breaches, the company also denied a breach of Clause 9.1 and Clause 2, as it had maintained high standards and had not prejudiced patient safety.

PANEL RULING

The Panel noted the complainant was anonymous and non-contactable. As stated in the introduction to the Constitution and Procedure such complaints were accepted and like all complaints, judged on the evidence provided by both parties. Complainants had the burden of proving their complaint on the balance of probabilities.

The Panel noted the complainant had received a promotional email for Relvar and was concerned GlaxoSmithKline was 'trying to hide important safety information, having seen their advertising in a number of places (internet, stand at conference, e-mail, letter)'.

The Panel noted that the sentence in the DTB highlighted by the complainant was within the section headed 'Unwanted effects' and stated 'Although pneumonia is more common in patients with chronic obstructive pulmonary disease (COPD) it has been reported in patients receiving fluticasone/vilanterol for asthma. The company is required to conduct a further study into the risk of pneumonia as an obligatory post-authorisation measure'.

The Panel noted the complainant's concern that GlaxoSmithKline was trying to hide important safety information on pneumonia as a side effect associated with using Relvar to treat asthma. The email provided by the complainant specifically highlighted pneumonia as a side effect associated with COPD but not asthma. GlaxoSmithKline stated that the clinical picture and management considerations for pneumonia in COPD patients was different to that in asthma. COPD patients were at higher risk of developing CAP than those in the general population and those with asthma. COPD patients with pneumonia had also been shown to have worse clinical outcomes compared with similarly aged pneumonia patients without COPD in terms of pneumonia severity, intensive care admissions, and mortality (Restrepo *et al*, 2006). GlaxoSmithKline further explained that the rates of pneumonia seen in COPD were significantly higher than the rates seen in asthma patients, including, importantly, rates of serious and severe events. This was expected based on the different disease profiles and the differing prognoses for pneumonia in the two conditions. That pneumonia was a more important clinical condition in COPD compared with asthma was highlighted by UK and international guidelines. The Panel also noted the Cochrane Review report on inhaled steroids and risk of pneumonia in COPD, Kew *et al* 2014, concluded that budesonide and fluticasone delivered as monotherapy or in combination with a LABA were associated with increased risk of a serious adverse pneumonia event but neither significantly effected mortality compared with controls. The safety concerns highlighted in the review should be balanced with recent cohort data and established evidence of efficacy regarding exacerbations and quality of life.

The Panel noted the submission from GlaxoSmithKline that although pneumonia was more common and seen to be a greater clinical challenge in COPD, it was also reported as a known adverse event associated with ICS/LABA use in asthma. GlaxoSmithKline submitted that overall, the incidence of pneumonia in asthma was low (≤1.1%) in all treatment groups. The Panel also noted GlaxoSmithKline's submission about the absolute

number of patients. The highest incidence of 1.1% for Revlar 200/25 corresponded to five patients. Nonetheless, the Panel noted GlaxoSmithKline's submission that pneumonia was correctly described as a common adverse event in the SPC. The Panel noted the concerns raised about pneumonia in the Discussion of Clinical Safety section of the EMA Revlar assessment report. The Panel noted that the regulators required GlaxoSmithKline to continue to gather information to further characterise the risk associated with Relvar (a combination of new chemical entities) in both asthma and COPD compared with other licensed ICS/LABAs.

The Panel examined the materials provided by both the complainant and GlaxoSmithKline. The email heading introduction to SMC guidance, part of the AWMSG advice section, and the reference to the Relvar website was missing from the material provided by the complainant. The email started with SMC guidance on the use of Relvar for asthma. The indication was given and the outcome of a study comparing Relvar with another ICS/LABA. The next section reported the AWMSG decision regarding use in COPD. The third section gave information about Relvar including, *inter alia*, it was generally well-tolerated in asthma. A similar statement about COPD was followed by details of the risk of pneumonia in COPD. The prescribing information listed pneumonia as a common side effect. The precautions section of the prescribing information gave details of an increased incidence of pneumonia in COPD patients receiving Relvar.

The Panel did not consider that mentioning pneumonia in relation to COPD patients in the email meant that it did not have to be considered in asthma patients. The Panel noted GlaxoSmithKline's comments about the importance of pneumonia in COPD compared to asthma. On balance, the Panel considered that it was therefore not unreasonable to mention pneumonia in relation to COPD alone. The Panel considered that the failure to discuss pneumonia in asthma did not mean that the email misled either directly or by implication. It was sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine. The information and claims about adverse reactions reflected current evidence and were capable of substantiation. The Panel did not consider GlaxoSmithKline had hidden pneumonia as a side-effect associated with Relvar in patients with asthma as alleged. No breach of Clauses 7.2, 7.4 and 7.9 was ruled.

The Panel noted the complainant was concerned that GlaxoSmithKline had not compared Relvar to Fostair, which was recently licensed for COPD. The complainant believed Fostair was commonly used to treat COPD and the Fostair information stated that pneumonia was uncommon. The Panel noted the claim in the email stated, 'Relvar is generally well tolerated in COPD. The risk of pneumonia in COPD patients with Relvar 92/22mcg is similar to that reported within the Summary of Product Characteristics of other commonly used ICS/LABAs'. The claim was referenced to the Relvar, Seretide and Symbicort Turbohaler SPCs and to Drainsfield *et al* 2013 which looked at Relvar in COPD. The data submitted by GlaxoSmithKline stated that the most commonly prescribed ICS/LABAs in the UK for COPD were Seretide and Symbicort (June 2013 – June 2014) and that clinicians would be familiar with prescribing them. GlaxoSmithKline stated that Fostair received a marketing authorization in COPD in 2014 and contained a different steroid component, beclometasone, to Seretide, Symbicort or Relvar. The Panel noted the data submitted by GlaxoSmithKline. The FORWARD study (Wedzicha *et al*, 2014), showed that pneumonia occurred in 3.8% of Fostair patients vs 1.8% in the formoterol (LABA alone) group and concluded 'The [Fostair] treatment arm was also associated with a higher incidence of pneumonia. This is in line with recent studies showing a 2-3 fold excess of pneumonia in the ICS/LABA treatment arms of studies compared to the corresponding monotherapy.' Calverley 2010 reported pneumonia in 2.1% of Fostair patients, 2.9% of Symbicort patients and 0.4% in the formoterol group and concluded: 'The rate of reported pneumonia was similar to that reported in placebo controlled trials using budesonide.' GlaxoSmithKline submitted that the association of pneumonia with ICS in COPD was regarded as a class effect and therefore similar risks of pneumonia could be expected with Relvar, Seretide, Symbicort and Fostair.

The Panel noted the complainant was uncontactable and had not provided any information to support his/her view that Fostair was commonly used to treat COPD. The Panel noted from the Fostair 100/6 SPC that Fostair was indicated in COPD for symptomatic treatment of patients with severe COPD (FEVI <50% predicted normal) and a history of repeated exacerbations. Pneumonia was listed as an uncommon (≥1/1000 and <1/100) undesirable effect in the SPC which was said to be derived from clinical trials in asthmatic and COPD patients. The SPC included an asterisk next to pneumonia and the explanation 'one related non serious case of pneumonia was reported by one patient treated with Fostair in a pivotal clinical trial in COPD patients'.

The Panel noted the complaint was received in August. The mail referred to the SMC decision in April 2014 and that AWMSG would be discussing, Relvar in asthma in July 2014. The Panel noted the data provided by GlaxoSmithKline showed that Fostair was not commonly prescribed for COPD around that time. There was a difference in indications. Fostair was only licensed for severe COPD. Although there appeared to be a difference between Fostair and Relvar with regard to whether pneumonia in COPD was common or uncommon as an undesirable effect in the SPCs, the data submitted by GlaxoSmithKline appeared to support similarities between the products. On the evidence before it the Panel did not consider the comparison was misleading and at the time the email was sent GlaxoSmithKline had not 'cherry picked' the information as alleged. No breach of Clauses 7.2, 7.3 and 7.10 was ruled. The claim was capable of substantiation. No breach of Clause 7.4 was ruled.

The Panel then considered the allegation about the GlaxoSmithKline website and the screen shot provided by the complainant.

The Panel noted GlaxoSmithKline's submission that the complainant had highlighted information in the section of the website for Budget Holders where three options were provided: 'Making a formulary application in asthma', 'Making a formulary application in COPD' and 'Need a quick reference guide for a formulary application for Relvar Ellipta'. The screen shots provided by the complainant appeared to come from the section 'Need a quick reference guide for a formulary application for Relvar Ellipta'.

The complainant highlighted two parts of a section headed 'safety profile'. These being:

> 'in common with other ICS – containing medicines there is an increased risk of pneumonia in COPD patients treated with Relvar 92/22mcg. The risk of pneumonia with Relvar 92/22mcg is similar to that reported within the Summary of Product Characteristics of other commonly used ICS/ LABAS licenced for the treatment of COPD.
>
> Pneumonia occurred in 6% of patients receiving Relvar 92/22mcg with 3% of patients receiving Vilanterol alone. The number of pneumonia events per 1000 patient years was 85.7 with OD Relvar, 92/22mcg and 42.3 with OD Vilanterol 22mcg.'

The Panel also noted that the section of the website provided by GlaxoSmithKline was headed 'Formulary Application Guide' and included links to the prescribing information as well as the SPCs.

GlaxoSmithKline submitted that a less detailed, top-line summary was provided of the indications and the key efficacy conclusions. As a result, less safety information was provided with it being stated that Relvar was generally well tolerated in asthma and COPD. For the reasons given above, further detail was, however, provided for pneumonia in COPD including incidence rates.

The Panel noted the section 'Making a formulary application in asthma' contained a detailed overview of the efficacy and safety data in asthma, within this section was an adverse events table which listed pneumonia as the first common adverse event within the 'System organ class' of 'Infection and infestations'. Below this table a section entitled 'Pneumonia' stated:

> 'In clinical trials of asthma patients the incidence of pneumonia seen with Relvar 92/22mcg was similar to that of placebo. There was a higher incidence of pneumonia with the 184/22mcg compared to the 92/22mcg strength. Few of the pneumonia events lead to hospitalisation with either strength. The number of pneumonia events per 1,000 patient years was 18.4 for fluticasone furoate/vilanterol (Relvar) 184/22mcg vs 9.6 for fluticasone furoate/vilanterol (Relvar) 92/22mcg and 8.0 in the placebo group (<1% overall).'

The Panel noted its comments and rulings above. Bearing in mind that detailed information was provided about pneumonia in asthma in the section 'Making a formulary application in asthma' (as well as pneumonia and COPD in the section 'Making a formulary application in COPD') and each section included links to the prescribing information and SPCs, the Panel considered that information on pneumonia as a side-effect in patients with asthma was available. The Panel did not consider that the section of the website for budget holders 'Need a quick reference guide for a formulary application for Revlar Ellipta' was misleading about the incidence of pneumonia in asthma nor did it fail to reflect the available evidence as alleged. No breach of Clauses 7.2, 7.4 and 7.9 was ruled.

The Panel did not consider that GlaxoSmithKline had failed to maintain high standards or had brought discredit on the pharmaceutical industry. Thus the Panel ruled no breaches of Clauses 9.1 and 2.

Complaint received **18 August 2014**

Case completed **13 November 2014**