CASE AUTH/3260/10/19

COMPLAINANT V GLAXOSMITHKLINE

Promotion of Trelegy

A complainant who described him/herself as a concerned UK health professional, complained about an advertisement (ref UK/TLY/0035/17K) for Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol) placed on the Primary Care Respiratory Society website by GlaxoSmithKline UK Limited in November 2018. The advertisement depicted the Trelegy inhaler in the bottom right hand corner of the screen. In the centre of the screen was the headline 'Less to take. More to take in'. This was followed by the two claims 'The only COPD triple therapy delivered in a single daily inhalation' and 'Improvement in quality of life vs ICS/LABA'.

The complainant noted that the claim 'Improvement in quality of life vs ICS/LABA' referenced the FULFIL clinical trial (Lipson et al 2017) which only compared Trelegy Ellipta with AstraZeneca's Symbicort Turbohaler (budesonide (ICS)/formoterol (LABA)); no other ICS/LABA combination was assessed. The complainant stated that, in essence, the claim was very general whereas the evidence base was very specific.

The detailed response from GlaxoSmithKline is given below.

The Panel considered that the claim that Trelegy Ellipta demonstrated 'Improvements in quality of life vs ICS/LABA' unequivocally implied that the medicine improved quality of life in COPD patients compared with all ICS/LABA combinations. The Panel noted that the claim was referenced to the FULFIL clinical trial (Lipson et al 2017) which compared Trelegy Ellipta with AstraZeneca's Symbicort Turbohaler (budesonide (ICS)/formoterol (LABA)). The Panel noted GlaxoSmithKline's submission that FULFIL was the only trial referenced alongside the claim because it was the main study which referenced QoL as a primary endpoint.

The Panel noted that the complainant had stated that the study cited in support of the claim was very specific whereas the claim was general. In that regard, the Panel noted that, where references were required, companies did not have to cite every study which supported a claim but they must be able to substantiate the claim and provide the relevant data if called upon to do so.

In the Panel's view, the claim for Trelegy Ellipta of 'Improvement in quality of life vs ICS/LABA' implied that there was evidence to support an improvement in QoL with Trelegy Ellipta when compared with all ICS/LABA combinations for COPD which was not so. The Panel noted that with regard to QoL Trelegy Ellipta had been directly and favourably compared with budesonide/formoterol in the FULFIL study (primary endpoint) and with fluticasone/valenterol in the IMPACT study (secondary outcome). The Panel noted, however, that Calverley et al (2010) compared Fostair (beclomethasone/formoterol) with Symbicort (budesonide/formoterol) rather than Trelegy

Ellipta and showed Fostair to be non-inferior to Symbicort in terms of QoL improvement. There was thus only indirect evidence to show that Trelegy Ellipta would be likely to improve QoL more than beclomethasone/formoterol based on the data extrapolated from Caverley et al (2010). The Panel considered that although there was favourable data with regards to QoL for Trelegy Ellipta from direct comparisons with some of ICS/LABA combinations, it was not clear that with regards to Fostair, the claim was based on extrapolated data. There was also no data with which to compare Trelegy Ellipta and fluticasone propionate/salmeterol (eg GlaxoSmithKline's Seretide).

The Panel considered that the claim did not reflect the evidence clearly and that the comparison was misleading and incapable of substantiation and breaches of the Code were ruled.

A complainant who described him/herself as a concerned UK health professional, complained about an advertisement (ref UK/TLY/0035/17K) for Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol) placed on the Primary Care Respiratory Society website by GlaxoSmithKline UK Limited in November 2018. The advertisement depicted the Trelegy inhaler in the bottom right hand corner of the screen. In the centre of the screen was the headline 'Less to take. More to take in'. This was followed by the two claims 'The only COPD triple therapy delivered in a single daily inhalation' and 'Improvement in quality of life vs ICS/LABA'. Trelegy Ellipta was indicated as maintenance treatment in adults with severe chronic obstructive pulmonary disease (COPD) who were not adequately treated with dual therapy ie a long-acting B_2-agonist combined with either a muscarinic agonist or an inhaled corticosteroid. Trelegy was triple therapy and combined an inhaled corticosteroid (ICS) (fluticasone furoate), a long-acting B_2-agonist (LABA) (vilanterol) and a long-acting muscarinic receptor agonist (LAMA) (umeclidinium).

COMPLAINT

The complainant noted that the claim 'Improvement in quality of life vs ICS/LABA' referenced the FULFIL clinical trial (Lipson *et al* 2017) which only compared Trelegy Ellipta with AstraZeneca's Symbicort Turbohaler (budesonide (ICS)/formoterol (LABA)); no other ICS/LABA combination was assessed. The complainant stated that, in essence, the claim was very general whereas the evidence base was very specific.

When writing to GlaxoSmithKline, the Authority asked it to consider the requirements of Clauses 7.2, 7.3 and 7.4 of the Code.

RESPONSE

GlaxoSmithKline stated that the claim was substantiated by the quality of life (QoL) data from the FULFIL clinical trial. The company did not know of any data to suggest that the claim was not correct and the complainant had not suggested that any such data existed.

The FULFIL clinical trial was pivotal in the evidence submission that led to the Medicines and Healthcare products Regulatory Agency (MHRA) and the European Medicines Agency (EMA) granting a licence for Trelegy Ellipta in patients not adequately controlled by an ICS/LABA, ie the whole class of medicines (ICS/LABA).

The FULFIL trial compared Trelegy Ellipta with Symbicort Turbohaler. The regulators accepted Symbicort as an appropriate comparator to represent the ICS/LABA class, as a well-known, well understood medicine and the most commonly prescribed when the trial was conducted. The FULFIL trial demonstrated statistically significant QoL benefits for patients vs an ICS/LABA ie Symbicort Turbohaler. QoL was a co-primary endpoint within the trial and as such was seen as robust evidence to qualify the QoL claim, along with the knowledge that, when the trial was conducted, Symbicort was the ICS/LABA most likely to be prescribed.

GlaxoSmithKline further submitted that the claim was further supported by additional data from the Trelegy Ellipta summary of product characteristics (SPC) also referenced in the advertisement in question, ie the IMPACT trial (Lipson *et al* 2018). Additionally, the Fostair registration clinical trial data (Calverley *et al* 2010) further supported the claim as explained below:

- The IMPACT clinical trial specifically showed a clinical improvement in QoL for Trelegy Ellipta vs Relvar Ellipta (fluticasone furoate/vilanterol), another commonly prescribed ICS/LABA.
- Fostair (beclomethasone/formoterol), another commonly prescribed ICS/LABA, had further been shown to be non-inferior in terms of QoL improvement vs Symbicort.

Triple therapy medicines (including Trelegy Ellipta) were further recognised by the National Institute for Health and Care Excellence (NICE) 2019 (the management of COPD in primary and secondary care) and The Global initiative for chronic Obstructive Lung Disease (GOLD) 2019 strategy document as a treatment option that had the potential to improve QoL (as measured by severity and frequency of symptoms) in patients who were not adequately controlled by ICS/LABAs. Both documents referred to the class of medicines and not individual medicines.

Relvar Ellipta (fluticasone furoate(ICS)/vilanterol(LABA)) contained two of the constituent molecules of Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol).

Background to COPD

GOLD 2019 highlighted the burden of COPD and stated:

> 'COPD is currently the fourth leading cause of death in the world but is projected to be the third leading cause of death by 2020. More than 3 million people died of COPD in 2012 accounting for 6% of all deaths globally. COPD represents an important public health challenge that is both preventable and treatable and is a major cause of chronic morbidity and mortality throughout the world.'

GlaxoSmithKline explained that typical symptoms of COPD included dyspnoea, chronic cough, sputum production and frequent lower respiratory tract infections. These symptoms could vary from day-to-day and could lead to disability and anxiety. COPD could have a profound impact on a patient's QoL, not only on his/her mental well-being, but also through the limitations that COPD symptoms, severity and exacerbations could have on his/her activities of daily living.

It was now widely understood that COPD impacted patients beyond just dyspnoea which was why the GOLD 2019 strategy document recommended a comprehensive assessment of symptoms rather than just a measure of breathlessness. GOLD 2019 quoted the most comprehensive disease-specific health status questionnaires as:

- The Chronic Respiratory Questionnaire (CRQ),
- St. George's Respiratory Questionnaire (SGRQ),
    - The SGRQ was a disease-specific questionnaire designed to measure the impact of respiratory disease and its treatment on a COPD patient's QoL. In addition to an overall summary (total) score, scores for the individual domains of Symptoms, Activity, and Impacts were produced. Scores ranged from 0 to 100, with lower scores indicating better QoL. Thus, a decrease in score indicated improvement in QoL.
- COPD Assessment Test (CAT) and
- The COPD Control Questionnaire (The CCQ).

These questionnaires were used in clinical trials to assess improvements in QoL, through change in scores from baseline to specific timepoints in the clinical trials.

Pharmacological treatment of COPD

In the UK, management of COPD treatment was determined by the NICE 2019 guidelines and the internationally recognised GOLD 2019 strategy document. NICE and GOLD advocated an approach to COPD diagnosis and management through assessment of severity and frequency of symptoms and risk of exacerbations. It was the frequency and severity of these symptoms and exacerbations that impacted the QoL for a COPD patient.

GlaxoSmithKline explained that COPD was typically treated using a combination of long-acting muscarinic antagonists (LAMAs), long-acting B_2-agonists (LABAs) and/or inhaled corticosteroids (ICSs). Patients were prescribed either two out of these three classes (eg ICS/LABA or LAMA/LABA), or a combination of all three (ie triple therapy). Both NICE and GOLD recommended triple therapy for those with significant symptoms (persistent exacerbations and breathlessness) despite treatment with bronchodilators (LAMA/LABA) or an ICS/LABA.

Triple therapy could be delivered in one or more inhalers. Trelegy Ellipta was a single inhaler triple therapy licensed for maintenance treatment in adults with moderate to severe COPD who were not adequately treated by an ICS/LABA combination or a LABA/LAMA combination.

GlaxoSmithKline explained that the FULFIL study was a European Phase IIIa, randomised, double-blind registration trial to support the efficacy and safety of Trelegy Ellipta vs Symbicort Turbohaler; the results were published in a peer-reviewed journal (Lipson *et al* 2017).

There were 1,810 patients in the 24-week trial a subset of whom (n=430) were treated for up to 52 weeks in an extension of the study. The co-primary efficacy endpoints were change from baseline in trough forced expiratory volume in one second (FEV_1), a measure of pulmonary function commonly used in clinical trials to measure treatment effectiveness and change from baseline in the SGRQ total score at week 24. A decrease in SGRQ score indicated improvement in quality of life.

Symbicort Turbohaler was the most commonly prescribed ICS/LABA combination for COPD in the UK when the FULFIL trial was conducted. Other ICS/LABAs included Fostair (beclomethasone/formoterol), Seretide Accuhaler (fluticasone propionate/salmeterol) and Relvar Ellipta (fluticasone furoate/vilanterol). The evidence for this could be seen in the budget impact model (BIM) using a data pack for 12 months up to September 2016 (copy provided). (The FULFIL trial completed on 7 April 2016.) The data pack showed that an estimated 1.337m units of Fostair 100/6; 2.040m units of Symbicort (200/6 and 400/12), 1.869m units of Seretide Accuhaler 500 and 0.420m units of Relvar Ellipta 92/22 were used in COPD.

GlaxoSmithKline explained that the prescribing data used in the BIM was publicly available. The BIM used an extract provided by GlaxoSmithKline Commercial Analytics. The values used for the proportions of products used in COPD and also for pack collection rates was sourced from a third party data provider which could run analysis using representative samples of GP practice systems to generate the estimate.

The FULFIL trial demonstrated a clinically meaningful and statistically significant improvement vs Symbicort Turbohaler over baseline of 2.2 units at week 24 in SGRQ score, in favour of Trelegy Ellipta ($p<0.001$).

The FULFIL trial was pivotal in the evidence submission that led to the MHRA and EMA granting a licence for use of Trelegy in patients not adequately controlled by an ICS/LABA (ie the whole class of medicines), accepting Symbicort as an appropriate comparator to represent the ICS/LABA class.

The IMPACT clinical trial was a Phase III, 52 week, randomised, double-blind, 3-arm parallel group study, which compared the efficacy, safety and tolerability of Trelegy Ellipta vs Relvar Ellipta (fluticasone furoate/vilanterol) (ICS/LABA), and Anoro Ellipta (umeclidinium/vilanterol) (LAMA/LABA). The trial was conducted in 37 countries with the results published in a peer reviewed journal and cited in the Trelegy Ellipta SPC. The primary endpoint was the annual rate of moderate or severe COPD exacerbations during treatment. Secondary outcomes included lung function, symptoms, the time to the first exacerbation and the change in the SGRQ total score to assess QoL.

The intention-to-treat population included 10,355 patients. Trelegy Ellipta resulted in a lower rate of moderate or severe COPD exacerbations than Relvar Ellipta or Anoro Ellipta. For the mean change from baseline in trough FEV_1, the differences between Trelegy Ellipta and Relvar Ellipta and Anoro Ellipta were statistically significant. The study further found significant differences between Trelegy Ellipta and the Relvar Ellipta and Anoro Ellipta groups with the mean change from baseline in the SGRQ total score and in the percentage of patients who had a response as defined by a decrease in the SGRQ total score of at least 4 points ($p<0.001$ for both comparisons on both outcomes). GlaxoSmithKline noted that a difference of 4 points was defined as the minimal clinically important difference. A statistically significant mean change of 1.8 units in SGRQ score was found in favour of Trelegy Ellipta vs Relvar Ellipta ($p<0.001$).

In summary, the IMPACT trial showed that once-daily triple therapy with Trelegy Ellipta (ICS/LABA/LAMA) resulted in a better QoL than dual therapy with Relvar Ellipta (ICS/LABA) and Anoro Ellipta (LAMA/LABA).

Calverley *et al* (2010) investigated the efficacy and safety of Fostair (beclomethasone/formoterol) (ICS/LABA) vs Symbicort (budesonide/ formoterol) (ICS/LABA)

and Oxis (formoterol) (LABA). The hypotheses tested was that Fostair was non-inferior to Symbicort in terms of the change in pre-dose morning FEV_1 from baseline to 48 weeks and that Fostair was superior to Oxis alone in terms of the mean rate of COPD exacerbations per patient per year. This clinical trial was published in a peer-reviewed journal. The clinical trial was a double-blind, double-dummy, randomised, active-controlled, parallel-group study with 703 patients. Co-primary endpoints were change from baseline to 48 weeks in pre-dose morning FEV_1 and mean rate of COPD exacerbations.

Calverley *et al* demonstrated that Fostair was not inferior to Symbicort and was superior to Oxis. The overall rate of COPD exacerbations per patient per year was similar and not statistically significantly different among treatments. QoL and COPD symptoms improved in all groups and use of rescue medication decreased. The trial demonstrated that Fostair was not inferior to Symbicort, including with regard to improvements to QoL.

GlaxoSmithKline noted the claim that Trelegy Ellipta demonstrated improvements in quality of life vs ICS/LABA. As explained above, COPD was typically treated using a combination of ICS/LABA or LAMA/LABA, or all three classes (ie triple therapy) (ICS/LAMA/LABA) for those not adequately treated by dual therapy. The claim therefore compared medicines for the same needs. QoL was further a material and relevant measure of the effectiveness of these treatments. The comparison was substantiated by the following:

1 The FULFIL clinical trial in which Trelegy Ellipta achieved a statistically significant improvement in health-related quality of life data (measured using SGRQ score) compared with Symbicort Turbohaler.

2 The FULFIL trial was pivotal in the evidence submission that led to the MHRA and EMA granting a licence for use of Trelegy in patients not adequately controlled by an ICS/LABA (i.e. the whole class of medicines). Symbicort was accepted as an appropriate comparator to represent the ICS/LABA class (which representation was further supported by the Fostair registration study, in which Fostair was found to be non-inferior to Symbicort with regards to improvements in QoL).

3 FULFIL was the only trial referenced alongside the claim at issue because it was the main study which referenced QoL as a primary endpoint.

4 The IMPACT clinical trial referenced in the Trelegy Ellipta SPC compared Trelegy Ellipta with Relvar Ellipta another ICS/LABA. One of the secondary endpoints of the study was change in baseline SGRQ (ie. an improvement in health-related quality of life data); a statistically significant mean change of 1.8 units was found in favour of Trelegy Ellipta ($p<0.001$).

GlaxoSmithKline stated that it considered that the claim was adequately substantiated based on the reference provided and therefore it was not misleading. The medicines for the same needs were compared within the claim, and one or more material, relevant, substantiable and representative features were compared. GlaxoSmithKline denied a breach of Clauses 7.3 and 7.4.

GlaxoSmithKline considered that the claim that Trelegy Ellipta demonstrated improvements in quality of life vs ICS/LABA was accurate, fair and balanced because it reflected the FULFIL data, which was referenced adjacent to the claim, and data referenced in the Trelegy SPC.

When FULFIL was conducted, the most frequently prescribed ICS/LABA for COPD was Symbicort at 33%. Other ICS/LABAs included Seretide (30%), Fostair (22%) and Relvar Ellipta (6.8%).

When the advertisement was published in November 2018, the most frequently prescribed ICS/LABAs for patients with COPD was budesonide/formoterol at 33% (this included Symbicort and DuoResp Spiromax, which were both budesonide/formoterol ICS/LABA combinations; the patent for Symbicort had expired in 2018, hence the generic alternative availability and prescriptions). Other frequently prescribed ICS/LABA's were Fostair (32%), Relvar Ellipta (16%) and fluticasone propionate/salmeterol at 15% (this included Seretide, AirfluSal and Aerivio Spiromax, which were all fluticasone propionate/salmeterol ICS/LABA combinations).

GlaxoSmithKline stated that the data in FULFIL, IMPACT, and the Fostair registration studies was an up-to-date evaluation of all the evidence available when the advertisement was published. The claim 'improved QoL vs ICS/LABA' reflected the FULFIL and IMPACT data which were both in the Trelegy Ellipta SPC and referenced in the advertisement.

GlaxoSmithKline further submitted that the FULFIL trial was the key registration study upon which the Trelegy Ellipta licence was granted in November 2017 for the indication: '… maintenance treatment in adult patients with moderate to severe COPD who are not adequately treated by a combination of an ICS and a LABA …'. The EMA and MHRA therefore clearly accepted Symbicort as an appropriate comparator for the purposes of granting a general licence for use of Trelegy in patients not adequately treated by the class of ICS/LABAs, as opposed to patients not adequately treated by Symbicort (or budesonide/formoterol generics) specifically.

GlaxoSmithKline considered that the claim was based on an up-to-date evaluation of all of the evidence and reflected that evidence clearly. The claim was not misleading or an exaggeration and so the company denied a breach of Clause 7.2.

PANEL RULING

The Panel considered that the claim that Trelegy Ellipta demonstrated 'Improvements in quality of life vs ICS/LABA' unequivocally implied that the medicine improved quality of life in COPD patients compared with all ICS/LABA combinations. The Panel noted that the claim was referenced to the FULFIL clinical trial (Lipson *et al* 2017) which compared Trelegy Ellipta with AstraZeneca's Symbicort Turbohaler (budesonide (ICS)/formoterol (LABA)). The Panel noted GlaxoSmithKline's submission that FULFIL was the only trial referenced alongside the claim because it was the main study which referenced QoL as a primary endpoint.

The Panel noted that the complainant had stated that the study cited in support of the claim was very specific whereas the claim was general. In that regard, the Panel noted that, where references were required, companies did not have to cite every study which supported a claim but they must be able to substantiate the claim and provide the relevant data if called upon to do so.

The Panel noted GlaxoSmithKline's submission that when the advertisement was published in November 2018, the most frequently prescribed ICS/LABA combinations for COPD patients were budesonide/formoterol, as used in the FULFIL study, at 33% (this included Symbicort and DuoResp Spiromax) and beclomethasone/formoterol (Fostair) at 32%; fluticasone

furoate/vilanterol (Relvar Ellipta) accounted for 16% and fluticasone propionate/salmeterol (this included Seretide, AirfluSal and Aerivio Spiromax) accounted for 15%.

The Panel noted GlaxoSmithKline's submission that the FULFIL clinical trial was pivotal in the evidence submission that led to the MHRA and the EMA granting a licence for Trelegy Ellipta in patients not adequately controlled by an ICS/LABA, ie all ICS/LABAs. The Panel noted, however, that whilst the regulators had accepted Symbicort as an appropriate comparator to represent the ICS/LABA class for the purposes of a clinical trial and the granting of a licence, it did not mean that the results of the study were necessarily such as to support an all-embracing, promotional comparative claim against every ICS/LABA combination product available. The Panel noted that GlaxoSmithKline had also stated that the FULFIL study was a European Phase IIIa, randomised, double-blind registration trial to support the efficacy and safety of Trelegy Ellipta vs Symbicort Turbohaler.

The Panel noted GlaxoSmithKline's submission that the claim was further supported by additional data from the Trelegy Ellipta SPC, ie the IMPACT trial (Lipson *et al* 2018) and by the Fostair registration clinical trial data (Calverley *et al* 2010). According to GlaxoSmithKline the IMPACT clinical trial specifically showed a clinical improvement in QoL for Trelegy Ellipta vs Relvar Ellipta (fluticasone furoate/vilanterol). The Panel noted that the measurement of QoL was a secondary outcome in the IMPACT study. Calverley *et al* (2010) had shown Fostair (beclomethasone/formoterol) to be non-inferior in terms of QoL improvement vs Symbicort and thus the Panel noted that the comparison of Fostair vs Trelegy Ellipta relied upon by GlaxoSmithKline was indirect. GlaxoSmithKline stated that the data in FULFIL, IMPACT, and the Fostair registration studies was an up-to-date evaluation of all the evidence available when the advertisement was published.

The Panel noted that Clause 7.2 stated that information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis. Material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine. The Panel noted that Clause 7.3 stated that a comparison was only permitted in promotional material if, *inter alia*, it was not misleading. Clause 7.4 stated that any information, claim or comparison must be capable of substantiation.

In the Panel's view, the claim for Trelegy Ellipta of 'Improvement in quality of life vs ICS/LABA' implied that there was evidence to support an improvement in QoL with Trelegy Ellipta when compared with all ICS/LABA combinations for COPD which was not so. The Panel noted that with regard to QoL Trelegy Ellipta had been directly and favourably compared with budesonide/formoterol in the FULFIL study (primary endpoint) and with fluticasone/valenterol in the IMPACT study (secondary outcome). The Panel noted, however, that Calverley *et al* (2010) compared Fostair (beclomethasone/formoterol) with Symbicort (budesonide/formoterol) rather than Trelegy Ellipta and showed Fostair to be non-inferior to Symbicort in terms of QoL improvement. There was thus only indirect evidence to show that Trelegy Ellipta would be likely to improve QoL more than beclomethasone/formoterol based on the data extrapolated from Caverley *et al* (2010). The Panel considered that although there was favourable data with regards to QoL for Trelegy Ellipta from direct comparisons with some of ICS/LABA combinations, it was not clear that with regards to Fostair, the claim was based on extrapolated data. There was also no data with which to compare Trelegy Ellipta and fluticasone propionate/salmeterol (eg GlaxoSmithKline's Seretide).

The Panel considered that the claim did not reflect the evidence clearly and a breach of Clause 7.2 was ruled. The Panel considered that the comparison was misleading and incapable of substantiation and breaches of Clauses 7.3 and 7.4 were ruled.

Complaint received **14 October 2019**

Case completed **3 August 2020**