NO BREACH OF THE CODE

CASE AUTH/3331/4/20

COMPLAINANT v GLAXOSMITHKLINE

Promotion of Relvar in Pulse magazine

A complainant who described him/herself as a concerned UK health professional complained about an advertisement for Relvar Ellipta placed in the December edition of Pulse magazine by GlaxoSmithKline. Relvar Ellipta was a combination of an inhaled corticosteroid (ICS (fluticasone furoate)) and a long-acting beta2 agonist (LABA (vilanterol)).

The complainant alleged that the generic name was not next to the most prominent mention of the brand name and that what was claimed was not supported by current data. By implying it could improve 25% of patients it was exaggerating the use of the medicine since this was extrapolating from data that was already non-comparative and therefore should not be used to make comparisons.

The detailed response from GlaxoSmithKline is given below.

The Panel noted GlaxoSmithKline's submission that following the Panel ruling in Case AUTH/3229/7/19 and the undertaking given, GlaxoSmithKline withdrew the material at issue in this current complaint in December 2019. It appeared to the Panel that the complaint was in relation to the advertisement as it appeared online and the Panel therefore made its rulings in relation to the requirements for electronic advertisements The non-proprietary name appeared immediately below the headline introducing Relvar Ellipta on the first page of the double page spread and the Panel therefore ruled no breach of the Code.

The Panel noted that the advertisement included the claim 'Choosing Relvar could help 25% more patients improve asthma control vs other ICS/LABAs' which was followed by 'In a real-world study, ACT responders for Relvar were 70% vs. 56% for the other ICS/LABA arm; absolute difference 14%. Study had minimal exclusion criteria and minimal intervention.' The claim was referenced to Woodcock et al and contained the results of the Salford Lung Study.

The Panel noted that Section 5.1 of the Relvar SPC stated that no comparative studies versus salmeterol/FP or versus other ICS/LABA combinations had been conducted to appropriately compare the effects on asthma exacerbations. This section of the SPC also included data from a 24 week study in adult and adolescent patients demonstrating an overall improvement in lung function for both fluticasone furoate/vilanterol and salmeterol/FP; the adjusted mean treatment difference between the groups was not statistically significant. For trough FEV1 the difference in the mean change from baseline between the fluticasone furoate/vilanterol group and the salmeterol/FP group was not statistically significant. The same section of the SPC referred to a randomised, double-blind 24 week non-inferiority study in adults and adolescents in which subjects

randomised to fluticasone furoate/vilanterol maintained lung function comparable with those randomised to salmeterol/FP.

The Panel noted that the Salford Lung study referred to showed that the proportion of ACT responders was 70% for the Relvar arm and 56% for the comparator arm (usual care) and noted GlaxoSmithKline's submission that this absolute difference of 14% equated to 25% of the 56% of comparator responders and was how the figure of '25% more' was arrived at. The Panel noted that as far as the usual care group was concerned, no specific medicines (other than other ICS/LABA) or doses were identified in the study. However, there was a comparison of treatments and this was contrary to the allegation. The Panel considered that the claim was not misleading or exaggerated as alleged and the claim was substantiated by the study which included a comparison of Relvar with usual care. The Panel therefore ruled no breaches of the Code including that GlaxoSmithKline had not failed to maintain high standards.

A complainant who described him/herself as a concerned UK health professional complained about an advertisement for Relvar Ellipta placed in the December edition of Pulse magazine by GlaxoSmithKline. Relvar Ellipta was a combination of an inhaled corticosteroid (ICS (fluticasone furoate)) and a long-acting beta$_2$ agonist (LABA (vilanterol)).

Relvar Ellipta was indicated for, *inter alia*, the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicine was appropriate in patients not adequately controlled with ICS and as needed inhaled short- acting beta$_2$ agonist (SABA) or patients adequately controlled on both ICS and LABA.

COMPLAINT

The complainant provided a screenshot of the advertisement at issue and a link to it in the December 2019 issue of pulse online and stated that the generic name was not next to the most prominent mention of the brand name. The complainant cited Clauses 7.2, 7.3, and 7.4 and stated that what was claimed was not supported by current data. The complainant further cited Clause 7.10 and stated that by implying it could improve 25% of patients it was exaggerating the use of the medicine since this was extrapolating from data that was already non-comparative and therefore should not be used to make comparisons. The complainant also cited Clause 9.1.

When writing to GlaxoSmithKline, the Authority asked it to consider the requirements of Clauses 4.3, 7.2, 7.3, 7.4, 7.10 and 9.1 of the Code.

RESPONSE

GlaxoSmithKline submitted that the complainant, who wished to remain anonymous, had referred to a Relvar Ellipta advertisement (UK/FFT/0003/19) Relvar 2019 journal advertisement double page spread in the December 2019 issue of Pulse Magazine which was available to view online. The item was certified in March 2019 and the final form was reviewed electronically as a pdf within Zinc.

GlaxoSmithKline refuted the allegations and responded to the four concerns separately.

1 Clause 4.3 '*The generic name was not next to the most prominent mention of the brand name*'

GlaxoSmithKline stated that Clause 4.3 of the Code required that for electronic advertisements, the non-proprietary name of the medicine must appear immediately adjacent to the brand name at its first appearance in a size such that the information was readily readable. The advertisement in question satisfied this requirement as the generic name was immediately below the headline introducing Relvar Ellipta on the first page of the double page spread and was readily readable. GlaxoSmithKline denied the allegation of a breach of Clause 4.3.

2 Clauses 7.2, 7.3, 7.4 '*What was claimed was not supported by current data*'

GlaxoSmithKline submitted that the complainant had provided no detail on how the claim was not supported by the data, but could reassure the Panel that the claim was not misleading, it was an appropriate comparison which was capable of substantiation.

GlaxoSmithKline submitted that the opening sentence, 'Choosing Relvar could help 25% more patients improve asthma control vs other ICS/LABAs' had further detail immediately below it, 'In a real-world study, ACT [asthma control test] responders for Relvar were 70% vs. 56% for the other ICS/LABA arm; absolute difference 14%. Study had minimal exclusion criteria and minimal intervention'.

GlaxoSmithKline submitted that the study showed that the proportion of ACT responders was 70% for the Relvar arm and 56% for the comparator arm. This absolute difference of 14% equated to 25% of the 56% of comparator responders and was how the figure of '25% more' was arrived at. GlaxoSmithKline confirmed that this was a comparative study with one arm being Relvar and the other being usual care, with the commonly prescribed ICS/LABAs comparison, a pre-specified sub analysis.

As a real-world study, the objective was to see how the medicine performed outside the setting of a double-blind, double-dummy clinical trial, the study did indeed have minimal exclusion criteria and minimal intervention as noted in the publication. The publication stated, 'exclusion criteria were minimal, such as a recent history of life-threatening asthma, a history of COPD or concomitant life-threating disease' and 'in order to maintain the real-world nature of the study, patients' experience was kept as close to everyday clinical practice as possible'. Patients saw their usual healthcare providers and their medication was dispensed by community pharmacy in the usual manner. After randomisation, patients were only contacted by telephone on three occasions over 12 months to complete the ACT and a safety check, followed by an end of study visit. The ACT score was a validated tool to evaluate asthma control and was developed to provide an easy and quick tool to assess the multidimensional nature of asthma control. It was recognised by the Global Initiative for Asthma (GINA) guidelines and British Thoracic Society and Scottish Intercollegiate Guidelines Network (BTS/SIGN) as a symptom control tool for measuring asthma control.

GlaxoSmithKline submitted that what was claimed was supported by the data, was accurate, balanced, fair, objective, unambiguous and up to date and thus the company denied a breach of Clause 7.2.

Similarly, the comparison of Relvar versus other commonly used ICS/LABAs for the same indication was not misleading and thus GlaxoSmithKline denied a breach of Clause 7.3. Having provided the peer reviewed publication reference for the claim, it was clearly capable of substantiation and as such GlaxoSmithKline denied a breach of Clause 7.4.

3 Clause 7.10 '*By implying it could improve 25% patients it was exaggerating the use of the medicine since this was extrapolating from data that was already non-comparative and therefore should not be used to make comparisons*'

GlaxoSmithKline submitted that the data were comparative; there were two arms to the study and their results were compared. As outlined above, the results showed that the proportion of Asthma Control Test responders was 70% for the Relvar arm and 56% for the comparator arm. The absolute difference of 14% equated to 25% of the 56% of comparator responders and was how the figure of '25% more' was derived. This was not an extrapolation, but a simple calculation based on the figures from the study. It did not exaggerate and included the absolute rate of responders in each arm so the readers could be in no doubt what the results were.

4 Clause 9.1 Failure to maintain high standards

GlaxoSmithKline stated that following the Panel ruling in Case AUTH/3229/7/19, the company signed an undertaking on 5 December 2019. In order to consolidate all Relvar promotional materials, GlaxoSmithKline took a proactive approach to withdraw several related materials and the item in this current complaint was withdrawn from the publishers on 18 December 2019. GlaxoSmithKline received confirmation on 19 December 2019 that the item would no longer be used however it was issued by the publishers of Pulse Magazine on 19 December 2019.

GlaxoSmithKline submitted it had processes in place to ensure that promotional material was of a high standard. GlaxoSmithKline denied all allegations and did not believe it had failed to maintain high standards. GlaxoSmithKline denied the allegation of a breach of Clause 9.1.

In summary, this two-page journal advertisement accurately presented relevant clinical data from a real-world study, compared medicines that were both indicated in asthma and included the absolute percentage improvement of a recognised clinical endpoint measure of asthma control in a clear and unambiguous way. The complainant had provided no evidence or argument for any of their assertions and had incorrectly deemed the generic name to be wrongly positioned. As such GlaxoSmithKline submitted that the complainant had not discharged his/her burden of proof and the Panel should find in GlaxoSmithKline's favour on all points.

PANEL RULING

The Panel noted that as stated in the introduction to the Constitution and Procedure the complainant had the burden of proving there was a breach of the Code on the balance of probabilities.

The Panel noted GlaxoSmithKline's submission that following the Panel ruling in Case AUTH/3229/7/19 and the undertaking given, GlaxoSmithKline withdrew the material at issue in this current complaint in December 2019. GlaxoSmithKline received confirmation on 19 December 2019 that the item would no longer be used however it was issued by the publishers of Pulse Magazine on 19 December 2019.

Clause 4.3 stated that the non-proprietary name of the medicine or a list of the active ingredients using approved names where such exist must appear immediately adjacent to the most prominent display of the brand name in bold type of a size such that a lower case 'x' was no less than 2mm in height or in type of such a size that the non-proprietary name or list of active ingredients occupies a total area no less than that taken up by the brand name. For

electronic advertisements the non-proprietary name of the medicine or the list of active ingredients, as required by Clause 4.3, must appear immediately adjacent to the brand name at its first appearance in a size such that the information is readily readable.

The Panel noted GlaxoSmithKline's submission that the Relvar 2019 journal advertisement double page spread appeared in the December 2019 issue of Pulse Magazine which was available to view online. It appeared to the Panel that the complainant's allegation was in relation to the advertisement as it appeared online and the Panel therefore made its rulings in relation to the requirements for electronic advertisements The non-proprietary name appeared immediately below the headline introducing Relvar Ellipta on the first page of the double page spread as described by GlaxoSmithKline. The Panel therefore ruled no breach of Clause 4.3.

The Panel noted that the advertisement at issue included the claim 'Choosing Relvar could help 25% more patients improve asthma control vs other ICS/LABAs' which was followed by 'In a real-world study, ACT responders for Relvar were 70% vs. 56% for the other ICS/LABA arm; absolute difference 14%. Study had minimal exclusion criteria and minimal intervention.' The claim was referenced to Woodcock *et al* and contained the results of the Salford Lung Study.

The Panel noted the complainant's allegation that what was claimed was not supported by current data and that by implying it could improve 25% of patients it was exaggerating the use of the medicine since this was extrapolating from data that was already non-comparative and therefore should not be used to make comparisons.

The Salford Lung Study was an open-label randomised, two-arm effectiveness trial in patients aged 18 or over assigned randomly to initiate treatment with a once daily inhaled combination of 100 or 200mcg of fluticasone furoate with 25mcg vilanterol or continuation of optimised usual care (ICS alone or in combination with a LABA as maintenance therapy in usual care) and followed up for 12 months. The primary endpoint was the percentage of patients who achieved an asthma control test (ACT) score of 20 or greater or an increase in ACT score from baseline of 3 or greater at 24 weeks (termed responders) in patients with a baseline ACT score less than 20. Baseline assessments were collected, including assessment of asthma control using the ACT, information on disease duration, smoking status, concomitant medical history, various questionnaires relating to quality of life, work productivity, adherence, demographic information and information on concomitant medications. Patients were contacted by telephone at various time points and a study team member completed the ACT and assessed patients for adverse events or drug reactions. After 12 months a final assessment was done in person. There was no face to face contact with the study team between baseline and 12 month visits.

The ACT questions referred to the impact of asthma on work, school or home, frequency of shortness of breath, night time waking with symptoms, use of rescue medication and rating asthma control. All five questions related to the previous four weeks.

At week 24, the odds of being a responder were higher for patients who initiated treatment with fluticasone furoate and vilanterol than for those on usual care (odds ratio [OR] 2.00 [95% CI 1.70-2.34], $p<0.0001$). In patients for whom the general practitioner had found an ICS/LABA combination to be indicated for usual therapy, the odds of being a responder were also higher for those in the fluticasone furoate and vilanterol group than for those in the usual care group at week 24 (OR 1.95 [95% CI 1.60-2.38]). There was no statistically significant difference in the adjusted annual rate of severe exacerbations in patients initiated with fluticasone furoate and vilanterol compared with those continuing usual care.

The authors of the Salford Lung Study described the study limitations as perceived weaknesses which might relate to the open label design in routine care in the absence of regular face to face monitoring and the consequent potential for bias. A comparative effectiveness study required careful interpretation. Any bias might be enhanced by choosing a soft primary outcome, the ACT score whereby patients could indicate improvement merely as a result of being switched to a novel treatment. However in the authors' view that the benefit was present for the entire 52 week duration of the study indicated that this was not so. The authors stated that the unblinded nature of the study was the likely reason for the large degree of modification of treatment during the first 3 months in the fluticasone furoate and vilanterol group and that this modification was not due to loss of asthma control but mainly due to patients choosing to return to a long-standing treatment. The study concluded that 'patients in general practice with a diagnosis of symptomatic asthma had improved asthma control from the introduction of a simple once-daily combination treatment of fluticasone furoate and vilanterol without having any additional risk of serious adverse events'.

The Panel noted that Section 5.1 of the Relvar SPC stated that no comparative studies versus salmeterol/FP or versus other ICS/LABA combinations had been conducted to appropriately compare the effects on asthma exacerbations. This section of the SPC also included data from a 24 week study in adult and adolescent patients demonstrating an overall improvement in lung function for both fluticasone furoate/vilanterol and salmeterol/FP; the adjusted mean treatment difference between the groups was not statistically significant. For trough FEV1 the difference in the mean change from baseline between the fluticasone furoate/vilanterol group and the salmeterol/FP group was not statistically significant. The same section of the SPC referred to a randomised, double-blind 24 week non-inferiority study in adults and adolescents in which subjects randomised to fluticasone furoate/vilanterol maintained lung function comparable with those randomised to salmeterol/FP.

The Panel noted that the study referred to showed that the proportion of ACT responders was 70% for the Relvar arm and 56% for the comparator arm (usual care) and noted GlaxoSmithKline's submission that this absolute difference of 14% equated to 25% of the 56% of comparator responders and was how the figure of '25% more' was arrived at. The Panel noted that as far as the usual care group was concerned, no specific medicines (other than other ICS/LABA) or doses were identified in the study. However, there was a comparison of treatments and this was contrary to the allegation. The Panel considered that the claim was not misleading or exaggerated as alleged and the claim was substantiated by the study which included a comparison of Relvar with usual care. The Panel therefore ruled no breach of Clauses 7.2, 7.3, 7.4 and 7.10.

The Panel noted its rulings above and considered that in the particular circumstances of this case GlaxoSmithKline had not failed to maintain high standards and no breach of Clause 9.1 was ruled.

Complaint received **15 April 2020**

Case completed **5 October 2020**