CASE AUTH/3109/10/18

COMPLAINANT v ASTRAZENECA

AstraZeneca website

A complainant who described him/herself as a concerned UK health professional, complained about a number of companies' websites including that of AstraZeneca UK. The pages at issue concerned Forxiga (dapagliflozin), Onglyza (saxagliptin) and Symbicort (budesonide/formoterol). Forxiga and Onglyza were used in certain patients with type 2 diabetes mellitus and Symbicort was used in certain patients with asthma or chronic obstructive pulmonary disease (COPD).

The detailed response from AstraZeneca appears below.

1 Forxiga

The complainant alleged that significant space was given to weight loss and reduction in blood pressure on a Forxiga promotional website, and these were both unlicensed indications.

The Panel noted that Forxiga was used in certain adults with type 2 diabetes mellitus to improve glycaemic control. The indication wording in section 4.1 of the SPC referred to, *inter alia*, Section 5.1 which featured clinical study results which referred to weight and blood pressure reductions.

In that regard, the Panel considered that reference to weight and/or blood pressure reduction was not necessarily unacceptable as part of the promotion of Forxiga, however, context was important. In the Panel's view, any references to weight and/or blood pressure reduction must be clearly set within the context of the primary reason to prescribe Forxiga ie to improve glycaemic control.

The Panel noted that each section of the website where weight or blood pressure reductions with Forixga were referred to, stated in bold font that Forxiga was not indicated for weight loss or the management of high blood pressure. There were also references in these sections to weight change being a secondary endpoint in clinical trials. It appeared to the Panel that information with regard to weight and blood pressure was displayed directly after the HbA_{1c} data in the relevant sections, with the exception of the 'Pooled Data' section where weight reduction was presented alongside HbA_{1c} data.

In relation to the website as a whole, given the context within which the information on weight and blood pressure reductions appeared, the Panel did not consider that the information was presented in such a way as to suggest that it was the primary reason to prescribe Forxiga.

On balance, the information on weight and blood pressure reduction for Forxiga in the context of the website in question did not amount to the promotion of unauthorized indications as alleged and the Panel ruled no breaches of the Code.

2 Onglyza

The complainant highlighted a claim and alleged that the difference in HbA_{1c} reduction from baseline between Onglyza and sulphonylurea had been misrepresented.

The Panel noted that Goke *et al* stated that the mean changes from baseline HbA_{1c} were -0.74% vs. -0.80% with Onglyza vs glipizide [sulphonylurea], respectively. The Panel considered the layout of the graphic and the immediate impression to a health professional. The Panel noted that -0.74% was in much larger font relative to the rest of the graphic and it appeared directly below the wording 'Onglyza vs SU [sulphonylurea]'. In addition, the information in the text box below compared the number of hypoglycaemic events over two years between Onglyza and an SU.

In the Panel's view, the immediate impression was that -0.74% was the difference between Onglyza and sulphonylurea in change in HbA_{1c} from baseline, which was not so, and in that regard, it was a misleading comparison of the two medicines. The reference to the between-group difference, 0.06%, in very small font, was not sufficiently prominent and therefore did not negate the immediate misleading impression. Breaches of the Code were ruled including that AstraZeneca had failed to maintain high standards.

3 Symbicort

a) Use in COPD

The complainant alleged that exacerbations and symptom control had the relative rates of reduction displayed far more prominently than the absolute rate or indeed the co-primary endpoint that was not significantly different. The complainant also alleged that by stating that symptom control improved by 83%, AstraZeneca appeared to have intentionally ignored the non-significant endpoint of the study.

With regard to the exacerbation reduction webpage, in the Panel's view, the mention of the non-statistically significant co-primary result (FEV1) was disproportionate to the prominent representation of the co-primary result that showed statistical significance (number of severe exacerbations). The severe exacerbation rates with Symbicort Turbohaler vs formoterol (1.42 vs 1.84 per patient per year) were less prominently displayed than the relative risk reduction claim of 23%.

In the Panel's view, if relative risk reduction is stated, the absolute risk reduction should be presented

together with the relative risk reduction in such a way as to allow the reader to make an immediate assessment of the clinical impact of an outcome.

In the Panel's view, the 23% relative risk reduction in severe exacerbations for Symbicort Turbohaler vs formoterol was designed to be the primary take home message. The webpage highlighted, and placed disproportionate emphasis on, the relative risk reduction for one of the co-primary endpoints that had favoured AstraZeneca's product, without sufficient balance, and, in that regard, the immediate impression given by the webpage was a misleading comparison of Symbicort Turbohaler vs formoterol. Breaches of the Code were ruled including that AstraZeneca had failed to maintain high standards.

With regard to the symptom control webpage, the Panel noted that the primary endpoint of the study, PEF 5 minutes post-morning dose, was stated with a p-value of 0.603 which indicated that the difference observed between the two treatments was not statistically significant. The Panel noted that the main claim on the webpage related to a secondary endpoint, capacity of daily living (CDLM) score. The Panel considered that it was not unacceptable to present secondary endpoint data, as long as it was presented in the context of the primary endpoint results and with proportionate emphasis.

The Panel noted that the mean absolute change in CDLM score from baseline for both Symbicort Turbohaler and salmeterol/fluticasone (0.22 and 0.12, respectively) was mentioned on the webpage at issue, as was the difference between treatments of 0.10. The Panel noted the study authors' caution that, although statistically significant, the observed mean difference between treatments on this CDLM measure (0.10) was below the minimal important difference of 0.20.

In the Panel's view, the 83% relative improvement in total mean CDLM score for Symbicort Turbohaler vs salmeterol/fluticasone was designed to be the primary take home message. The webpage highlighted, and placed disproportionate emphasis on, the relative improvement of a secondary endpoint which favoured Symbicort Turbohaler, without sufficient balance, and, in that regard, the immediate impression given by the webpage was a misleading comparison of Symbicort Turbohaler vs salmeterol/fluticasone. Breaches of the Code were ruled including that AstraZeneca had failed to maintain high standards.

b) Use in asthma

The complainant alleged that the claim of a 39% reduction in exacerbations was not clear about what the absolute levels were; the seven times improvement in symptom control was again much more prominent than the absolute values and it was much harder to see that this was vs baseline and not vs alternate therapy.

With regard to exacerbation reduction, the Panel considered that there was no allegation with regard to the prominence of relative risk in relation to absolute risk. The Panel noted AstraZeneca's submission that the absolute figures for the claim in question were stated on the webpage. Based on the very narrow allegation the Panel ruled no breach of the Code.

With regard to symptom control, the Panel considered that it was sufficiently clear that the claim '7x more asthma control days vs baseline' was versus baseline and not versus the comparator arm and ruled no breaches of the Code in that regard.

The Panel noted that the % of asthma control days at baseline and following treatment were stated for both Symbicort SMART and salmeterol/fluticasone + SABA, with a statement that the result was similar between the two groups. The Panel noted that the claim of 7x more asthma control days was versus baseline and therefore it was not a claim of relative improvement vs a comparator medicine as alleged. Based on the narrow allegation it considered that the claim at issue was not misleading and ruled no breaches of the Code.

A complainant who described him/herself as a concerned UK health professional, complained about a number of companies' websites including that of AstraZeneca UK Limited. The pages at issue concerned claims about Forxiga (dapagliflozin), Onglyza (saxagliptin) and Symbicort (budesonide/formoterol). Forxiga and Onglyza were used in certain patients with type 2 diabetes mellitus and Symbicort was used in certain patients with asthma or chronic obstructive pulmonary disease (COPD).

AstraZeneca stated that its UK medicines website was intended for UK health professionals and this was indicated to those who visited the website. The content of the website had been created with this intended audience in mind.

AstraZeneca did not believe the webpages at issue were in breach of the Code; it had however removed access to the pages whilst awaiting the Panel's rulings.

1 Forxiga

COMPLAINT

The complainant provided a web address (https//medicines.astrazeneca.co.uk/home/diabetes/forxiga.html) and alleged that although weight was stated to be a secondary endpoint and Forxiga was not indicated, there was significant space given on a promotional website to something that was not a licensed indication. The complainant did not consider that merely stating that this was not licensed meant that AstraZeneca was allowed to promote it. The same approach was taken with reductions in blood pressure. The complainant asserted that if AstraZeneca wanted to promote, it had to obtain a marketing authorization. The complainant noted that as AstraZeneca had previously been reprimanded for off-licence promotion, it appeared that whatever sanctions were imposed were insufficient.

When writing to AstraZeneca, the Authority asked it to consider the requirements of Clauses 2, 3.2 and

9.1. The Authority also advised AstraZeneca that, in its view, the reference to insufficient sanctions was a statement about sanctions and not an allegation that there had been a breach of undertaking.

RESPONSE

AstraZeneca submitted that the indication for Forxiga, ie glycaemic control in adults with type 2 diabetes, was clearly stated at the top of the webpage. Immediately after this was the dosing section followed by information on the dapagliflozin clinical trial data related to glycaemic control and HbA_{1c} reduction. Three graphs depicted HbA_{1c} control over several different studies to cover the breadth of clinical trial data and also long-term data on HbA_{1c} control was presented.

Weight was an important consideration for diabetic patient management and was investigated as a secondary endpoint in the clinical development programme for dapagliflozin, since being established as a beneficial side effect of the medicine. The data was presented by baseline body mass index (BMI) and the subsequent weight loss in those groups compared with placebo from a randomised controlled trial. The reader, by clicking a relevant BMI group, was shown a graph representing the weight loss in that group over the time period of the study.

AstraZeneca submitted that the information was placed after the prominently displayed efficacy (HbA_{1c}) data and was clearly labelled as a secondary endpoint in the clinical trial. There was a prominent statement in a bold font stating that dapagliflozin was not indicated for weight loss. Blood pressure data was presented in a single chart following the weight loss data. Likewise, in this section, it was clearly stated that dapagliflozin was not indicated for blood pressure control. Cardiovascular indices (eg blood pressure) were important clinical considerations in the management of type 2 diabetics. As with weight loss, it had been established that similar to other sodium-glucose co-transporter 2 (SGLT2) inhibitors, dapagliflozin demonstrated a beneficial secondary benefit of blood pressure reduction.

In the weight loss and blood pressure sections, the reader was provided with a synopsis of the relevant clinical study, further allowing him/her to make an informed clinical decision.

AstraZeneca submitted that both the weight loss and blood pressure data had been provided in a considered manner, consistent with the data contained in the Forxiga summary of product characteristics (SPC). AstraZeneca denied that these sections of the website breached Clause 3.2; high standards had been maintained and as such there had been no discredit to, or reduction of, confidence in the pharmaceutical industry. AstraZeneca concluded that the material as approved for its intended purpose did not breach Clause 3.2 and thus it was also not in breach of Clauses 9.1 or 2.

Following a request for further information, AstraZeneca provided the full content of the Forxiga website.

PANEL RULING

The Panel noted that Clause 3.2 required that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its SPC. The supplementary information to this Clause, 'Unauthorized indications', stated that the promotion of indications not covered by the marketing authorization for a medicine was prohibited.

The Panel noted that Forxiga was indicated in adults with type 2 diabetes mellitus to improve glycaemic control as either a monotherapy when diet and exercise alone did not provide adequate glycaemic control in patients for whom use of metformin was considered inappropriate due to intolerance, or in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, did not provide adequate glycaemic control. The indication wording in Section 4.1 of the SPC referred to, *inter alia*, Section 5.1. The Panel noted that Section 5.1, Pharmacodynamic properties, featured clinical study results which referred to weight and blood pressure reductions.

In that regard, the Panel considered that reference to weight and/or blood pressure reduction was not necessarily unacceptable as part of the promotion of Forxiga, however, context was important. In the Panel's view, any references to weight and/or blood pressure reduction must be clearly set within the context of the primary reason to prescribe Forxiga ie to improve glycaemic control.

The Panel noted that the Forxiga website in question featured, *inter alia*, information regarding Forxiga's licensed indications, dosing, clinical trial data, real world evidence, data vs saxagliptin and data in combination with glucagon-like peptide (GLP) or insulin.

The Panel noted that information relating to reductions in weight and/or blood pressure with Forxiga were present in multiple sections throughout the website, and not only in the 'Clinical Trial Data' section provided by AstraZeneca in its initial response. The Panel noted that self-regulation relied upon, *inter alia*, full and accurate responses from companies. The Panel was concerned that it was only after a request from the Panel that AstraZeneca provided the full website content which included information on weight reduction with Forxiga in the 'Real World Evidence', 'Pooled Data', 'Forxiga vs saxagliptin' and 'Forxiga in combination with GLP or insulin' sections of the website. There was also further information regarding blood pressure reduction with Forxiga in the 'Real World Evidence' section.

The Panel noted that in each section of the website above, where weight or blood pressure reductions with Forixga were referred to, it was stated in bold font that Forxiga was not indicated for weight loss or the management of high blood pressure. There were also references in these sections to weight change being a secondary endpoint in clinical trials. It appeared to the Panel that the information with regard

to weight and blood pressure was displayed directly after the HbA_{1c} data in the relevant sections, with the exception of the 'Pooled Data' section where weight reduction was presented alongside HbA_{1c} data.

In relation to the website as a whole, in the Panel's view, given the context within which the information on weight and blood pressure reductions appeared, the Panel did not consider that the information was presented in such a way as to suggest that it was the primary reason to prescribe Forxiga.

The Panel noted its comments above and considered that, on balance, the information on weight and blood pressure reduction for Forxiga in the context of the website in question did not amount to the promotion of unauthorized indications as alleged and no breach of Clause 3.2 was ruled. AstraZeneca had not failed to maintain high standards in this regard and no breach of Clause 9.1 was ruled. The Panel thus ruled no breach of Clause 2.

2 Onglyza

COMPLAINT

The complainant provided a web address (https//medicines.astrazeneca.co.uk/home/diabetes/onglyza.html) and noted that the claim regarding Onglyza vs sulphonylurea had a graphic indicating 0.74% which he/she assumed was the difference between the two as indicated in the title. However, in much smaller writing the complainant noticed that the difference was in fact 0.06%. The complainant thought that the difference had been misrepresented.

When writing to AstraZeneca, the Authority asked it to consider the requirements of Clauses 7.2, 7.3 and 9.1.

RESPONSE

AstraZeneca submitted that this section of the website was intended to address health professionals' questions about the comparison of sulphonylureas and dipeptidyl peptidase – 4 (DPP4) inhibitors such as Onglyza. AstraZeneca explained that it had been clinically well established and acknowledged by health professionals that DPP4 inhibitors were not as efficacious as sulphonylureas in terms of HbA_{1c} reduction. However, health professionals were keen to know whether specific DPP4 inhibitors had comparable efficacy to sulphonylureas in this area and also demonstrated additional clinical relevant attributes (eg decreased incidence of hypoglycaemia).

With this in mind AstraZeneca noted that it had highlighted the reduction of HbA_{1c} vs baseline achieved by Onglyza in a non-inferiority study vs a sulphonylurea (Goke *et al* 2010). This figure was close to that achieved by the sulphonylurea in the study and was declared non-inferior. The reader was then led through the sulphonylurea comparison data and finally invited to read details of hypoglycaemic events in the study.

All of the information was accurate and was provided in one place and was given due prominence.

AstraZeneca denied breaches of Clauses 7.2, 7.3 and 9.1.

PANEL RULING

The Panel noted that the webpage at issue was titled 'Onglyza vs SU [sulphonylurea]*'. Below this title was an arrow shaped highlighted box which stated in large font '-0.74% HbA_{1c} reduction from baseline' and pointed to an adjacent second box, with a different background colour and smaller font, which stated ' … with Onglyza 5 mg at 1 year as add-on to metformin in a non-inferiority study vs a sulphonylurea (SU [glipizide mean dose 14.7 mg]) …vs -0.80%; between-group difference 0.06% (95% CI, -0.05% to 0.16%; n=858)[referenced to Goke *et al* 2010]. Below the two boxes was a third highlighted box which stated '10 times fewer hypoglycaemic events……over 2 years with Onglyza vs an SU (3.5% of patients and 38.4% of patients, respectively)' [referenced to Goke *et al* 2013]. Below the boxes was the footnote to the title which stated '*Onglyza 5 mg + metformin was considered non-inferior to glipizide + metformin as the upper limit of the 95% confidence [sic] of the treatment difference in the per protocol (PP) analysis was <0.35 at 1 year. Mean baseline HbA_{1c} of 7.5% for both groups. PP analysis: n=293 in each arm.'

The Panel noted the complainant's allegation that the difference in HbA_{1c} reduction from baseline between Onglyza and sulphonylurea had, given the 'Onglyza vs SU' title, been misrepresented as it appeared from the graphic to be -0.74% but it was in fact 0.06%.

The Panel noted that Goke *et al* stated that the mean changes from baseline HbA_{1c} were -0.74% vs. -0.80% with Onglyza vs glipizide [sulphonylurea], respectively. The Panel noted that the between-group difference of 0.06% was stated in the second box on the webpage at issue. The Panel considered the layout of the graphic and the immediate impression to a health professional. The Panel noted that -0.74% was in much larger font relative to the rest of the graphic and it appeared directly below the wording 'Onglyza vs SU'. In addition, the information in the text box below compared the number of hypoglycaemic events over 2 years between Onglyza and an SU. In the Panel's view, the immediate impression was that -0.74% was the difference between Onglyza and sulphonylurea in change in HbA_{1c} from baseline, which was not so, and in that regard, it was a misleading comparison of the two medicines. The reference to the between-group difference, 0.06%, in very small font, was not sufficiently prominent and therefore did not negate the immediate misleading impression. A breach of Clauses 7.2 and 7.3 were ruled. The Panel considered that AstraZeneca had failed to maintain high standards and ruled a breach of Clause 9.1.

3 Symbicort

b) Use in COPD

COMPLAINT

The complainant provided a web address (https//medicines.astrazeneca.co.uk/home/respiratory/symbicort-copd.html) and noted that exacerbations and symptom control had the relative rates of

reduction displayed far more prominently than the absolute rate or indeed the co-primary endpoint that was not significantly different. The complainant alleged that by stating that symptom control improved by 83%, AstraZeneca appeared to have intentionally ignored the non-significant endpoint of the study.

When writing to AstraZeneca, the Authority asked it to consider the requirements of Clauses 7.2, 7.3 and 9.1.

RESPONSE

AstraZeneca submitted that this portion of the website focused on key clinical attributes that health professionals would consider in relation to prescribing a combination inhaler such as Symbicort for COPD patients. One key goal of COPD therapy was to reduce exacerbations. The relative risk reduction in exacerbations was a more informative clinical measure than absolute risk reduction in a comparative clinical study. However, both were needed by a health professional to gauge the clinical relevance of exacerbation outcome reduction in a given study.

AstraZeneca noted that information adjacent to the claim in question stated:

> 'This study demonstrated that Symbicort Turbohaler increased FEV1 (co-primary endpoint) by 1% vs formoterol (n=208 and n=201 respectively; p=NS) and demonstrated a reduction in severe exacerbations with Symbicort Turbohaler 200/6µg vs formoterol 6 µg: 1.42 vs 1.84 severe exacerbations per patient per year, respectively.'

AstraZeneca submitted that the statement provided the absolute values for severe exacerbation reduction, allowing the health professional to contextualise the prominent relative risk reduction. The absolute figures were stated as the number of exacerbations per patient per year (second co-primary endpoint) on the website in text above. The absolute figures were provided after the outcome of the first co-primary endpoint result, to ensure the figures were read in the context of that result. The statement disclosed the fact that the first of the two co-primary endpoints was not statistically different. The second co-primary endpoint was statistically significant. AstraZeneca submitted that the statistical outcome of the first co-primary endpoint not being significant did not impact the validity of the second more clinically relevant outcome.

AstraZeneca thus considered that the information presented would be neither ambiguous nor misleading to the intended audience of health professionals; the company denied a breach of Clauses 7.2, 7.3 and 9.1.

AstraZeneca noted that symptom control was another goal of COPD therapy. In this regard the information adjacent to the claim in question stated:

> 'The primary outcome of increase in morning PEF [peak expiratory flow] at 5mins post dose was similar (mean difference 1.0l/min, p=0.603) between Symbicort 400/12 µg bd vs salmeterol/fluticasone 50/500 µg bd. The increase in morning FEV1, at 15 mins was higher for Symbicort Turbohaler compared to salmeterol/fluticasone (0.14L vs 0.10L, p<0.05). A secondary outcome variable showed relative improvement in total mean CDLM [Capacity of Daily Living during the Morning] score with Symbicort Turbohaler 400/12 µg twice daily vs salmeterol/fluticasone 50/500 µg twice daily (0.22 vs 0.12 respectively; 95% CI 0.01-0.19, p<0.05) when measured from baseline.'

AstraZeneca submitted that the first sentence made clear that the primary outcome between the two study arms was similar and reported the non-significant p-value. The text made it clear to the reader that the improvement in total mean CDLM was a secondary endpoint and the results were mentioned after the results of the primary endpoint. With respect to the absolute figures, AstraZeneca did not agree with the complainant because the absolute figures were clearly stated. As stated above, it was important for health professionals to understand the effect of medicines on symptoms and exacerbations to help make an informed decision for the management of COPD patients. In both the sections above AstraZeneca noted that it had stated the more clinically relevant relative risk reduction allowing the reader to establish the difference between the treatment groups, this was followed by the result of the primary endpoints, absolute figures and confidence intervals, to provide context.

AstraZeneca did not consider that the information presented was ambiguous or misleading to the intended health professional audience. The company denied breaches of Clauses 7.2, 7.3 and 9.1.

PANEL RULING

The Panel noted that the website at issue featured a section titled 'COPD and Symbicort'. The Panel noted that the complainant had made allegations with regard to two webpages. One webpage was titled 'Exacerbation reduction' and the other was titled 'Symptom Control'. The Panel noted that the complainant was concerned that the relative rates of reduction were displayed far more prominently than the absolute rates on these pages and more prominently than the non-significant co-primary endpoint on the exacerbation reduction webpage, and that the 83% relative improvement claim on the symptom control webpage seemed to intentionally ignore the non-significant endpoint of the study.

The Panel noted that Clause 7.2 required that information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis. The Panel noted that the supplementary information to Clause 7.2 stated that referring only to relative risk, especially with regard to risk reduction, could make a medicine appear more effective than it was. In order to assess the clinical impact of an outcome, the reader also needed to know the absolute risk involved. In that regard relative risk should never be referred to without also referring to

the absolute risk. Absolute risk could be referred to in isolation.

Exacerbation reduction webpage

The Panel noted that below the 'Exacerbation reduction' title was the statement 'Symbicort Turbohaler reduced the incidence of severe exacerbations* by 23% vs formoterol' which was in bold font and referenced to Szafranski *et al* (2003). Below the statement, to the left, was a large red circle containing a downward pointed arrow with the text '23% relative risk reduction in severe exacerbations (p=0.043)'. The '23%' was in much larger font compared to the rest of the text on the webpage. To the right of this red circle in less prominent text it stated:

> 'This study demonstrated that Symbicort Turbohaler increased FEV1 (co-primary endpoint) by 1% vs formoterol (n=208 and n=201 respectively; p=NS) and demonstrated **a reduction in severe exacerbations*** with Symbicort Turbohaler 200/6 µg vs formoterol 6 µg: 1.42 vs 1.84 severe exacerbations* per patient per year, respectively' [referenced to Szafranski *et al* 2003].

Below the red circle, the Szafranski *et al* (2003) study design details were provided, including the statement, 'Primary efficacy variables: number of severe exacerbations* and FEV1' and a footnote in relation to the asterisk which defined severe exacerbations.

The Panel considered that, in principle, when a co-primary endpoint failed to achieve statistical significance it was not necessarily unacceptable to refer to other co-primary endpoint data so long as this was placed within the context of the overall study findings. The nature of the material might also be relevant.

The Panel noted that the study authors stated in their analysis that it was required that both primary variables should give statistical significance at the 5% level in order to keep the overall significance level to 5% in the final conclusion. In this regard, the Panel queried the prominence and weight given to one of the two co-primary endpoints.

In the Panel's view, the mention of the non-statistically significant co-primary result (FEV1) was disproportionate to the prominent representation of the co-primary result that showed statistical significance (number of severe exacerbations). The severe exacerbation rates with Symbicort Turbohaler vs formoterol (1.42 vs 1.84 per patient per year) were less prominently displayed than the relative risk reduction claim of 23%.

In the Panel's view, if relative risk reduction is stated, the absolute risk reduction should be presented together with the relative risk reduction in such a way as to allow the reader to make an immediate assessment of the clinical impact of an outcome.

The Panel considered the immediate impression to a busy health professional; in its view, the 23% relative risk reduction in severe exacerbations for Symbicort Turbohaler vs formoterol was designed to be the primary take home message of the webpage. The webpage highlighted, and placed disproportionate emphasis on, the relative risk reduction for one of the co-primary endpoints that had favoured AstraZeneca's product, without sufficient balance, and, in that regard, the immediate impression given by the webpage was a misleading comparison of Symbicort Turbohaler vs formoterol. A breach of Clauses 7.2 and 7.3 was ruled.

The Panel considered that AstraZeneca had failed to maintain high standards and ruled a breach of Clause 9.1.

Symptom control webpage

The Panel noted that below the 'Symptom control' title was the statement 'Change in lung function and morning activities: Symbicort Turbohaler vs salmeterol/fluticasone from baseline'. Below the statement, to the left, was a large red circle containing an upwards pointed arrow with the text '83% relative improvement in total mean CDLM score* (P<0.05)' [referenced to Partridge *et al* 2009]. The asterisks had a footnote with the definition of CDLM. The '83%' was in a much larger font compared to the rest of the text on the webpage. To the right of the red circle in less prominent text it stated:

> 'The primary outcome of increase in morning PEF at 5mins post dose was similar (mean difference 1.0L/min, p=0.603) between Symbicort 400/12 µg bd vs salmeterol/fluticasone 50/500 µg bd'.

Below this was the statement, 'The increase in morning FEV1 at 15 mins was higher for Symbicort Turbohaler compared to salmeterol/fluticasone (0.14L vs 0.10L, p<0.05)', followed below by:

> 'A secondary outcome variable showed **relative improvement in total mean CDLM* score** with Symbicort Turbohaler 400/12 µg twice daily vs salmeterol/fluticasone 50/500 µg twice daily (0.22 vs 0.12 respectively; 95% CI 0.01-0.19, p<0.05) when measured from baseline. Mean difference (0.10 [95% CI, 0.01-0.19; p<0.05]). A change of 0.2 units of CDLM represents the minimal important difference. The GCSQ [Global Chest Symptoms Questionnaire] score secondary outcome variable showed no significant difference in treatment arms' [referenced to Partridge *et al* 2009].

At the bottom of the webpage at issue were details about the study design.

The Panel noted that the primary endpoint of the study, PEF 5 minutes post-morning dose, was stated on the webpage with a p-value of 0.603 which indicated that the difference observed between the two treatments was not statistically significant. The Panel noted that the main claim on the webpage related to a secondary endpoint, CDLM score. The Panel considered that it was not unacceptable to present secondary endpoint data, as long as it was presented in the context of the primary endpoint

results and with proportionate emphasis.
The Panel noted that the mean absolute change in CDLM score from baseline for both Symbicort Turbohaler and salmeterol/fluticasone (0.22 and 0.12, respectively) was mentioned on the webpage at issue, as was the difference between treatments of 0.10. The Panel noted the study authors' caution that, although statistically significant, the observed mean difference between treatments on this CDLM measure (0.10) was below the minimal important difference of 0.20.

In the Panel's view, if relative improvement is stated, the absolute improvement should be presented together with the relative improvement in such a way as to allow the reader to make an immediate assessment of the clinical impact of an outcome.

The Panel considered the immediate impression to a busy health professional; in the Panel's view, the 83% relative improvement in total mean CDLM score for Symbicort Turbohaler vs salmeterol/fluticasone was designed to be the primary take home message of the webpage. The webpage highlighted, and placed disproportionate emphasis on, the relative improvement of a secondary endpoint which favoured Symbicort Turbohaler, without sufficient balance, and, in that regard, the immediate impression given by the webpage was a misleading comparison of Symbicort Turbohaler vs salmeterol/fluticasone. A breach of Clauses 7.2 and 7.3 was ruled.

The Panel considered that AstraZeneca had failed to maintain high standards in this regard and ruled a breach of Clause 9.1.

b) Use in asthma

COMPLAINT

The complainant provided a web address (https3// medicines.astrazeneca.co.uk/home/respiratory/ symbicort-asthma.html) and noted that the claim of a 39% reduction in exacerbations was not clear about what the absolute levels were; the seven times improvement in symptom control was again much more prominent than the absolute values and it was much harder to see that this was vs baseline and not vs alternate therapy.

When writing to AstraZeneca, the Authority asked it to consider the requirements of Clauses 7.2, 7.3 and 9.1.

RESPONSE

AstraZeneca noted that a statement adjacent to the claim in question read:

> 'The total number of severe exacerbations was 208 and 125 for salmeterol/fluticasone + SABA and Symbicort SMART, respectively.'

AstraZeneca submitted that the information initially described the results of the primary endpoint, and then led the reader onto information about the secondary endpoints. The absolute figures for this claim (a secondary endpoint) were therefore clearly stated alongside the claim in context of the results of the overall study.
AstraZeneca did not consider that the information presented was mbiguous or misleading to the intended audience; the company denied breaches of Clauses 7.2, 7.3 and 9.1.

With regard to the claim '7 x more asthma control days vs baseline', AstraZeneca noted that the absolute figures were clearly stated in the adjacent information ie:

> 'Compared with their baseline, patients who received Symbicort SMART 200/6µg bd + additional inhalations as needed had a seven-fold increase in asthma control days (5.8% vs 41.3%).'

AstraZeneca submitted that with respect to the allegation that it was difficult to see that the claim was vs baseline, the words 'vs baseline' were clearly stated in the visual which contained the claim ('7 x more asthma control days vs baseline'). It was reinforced in the text adjacent to the visual (stated above). In addition, the title above the visual for this claim stated: 'Symptom control Improvement in asthma control days', to ensure that there was no ambiguity that this was not a comparative claim with an alternative medicine.' Furthermore, the results for salmeterol/fluticasone vs baseline were also presented to ensure the reader had sufficient clinical information and context of the overall results for this endpoint.

AstraZeneca thus did not consider that the information presented was either ambiguous or misleading, and it denied breaches of Clauses 7.2, 7.3 and 9.1.

PANEL RULING

The Panel noted that the website at issue featured a section titled 'Asthma ICS/LABAs and Symbicort'. The Panel noted that the complainant had made allegations with regard to two webpages. One webpage was titled 'Exacerbation reduction' and the other was titled 'Symptom Control'.

Exacerbation reduction

The Panel noted that below the 'Exacerbation reduction' title was the statement 'Symbicort SMART reduced the incidence of severe asthma exacerbations** by 39% vs salmeterol/fluticasone + SABA' [referenced to Kuna *et al* (2007)]. Below the statement, to the left, was a large red circle containing a downwards arrow and the statement '39% fewer severe exacerbations** vs salmeterol/ fluticasone + SABA ($p<0.001$)'. The '39%' was in much larger font than the rest of the text on this webpage. To the right of the red circle in less prominent text it stated:

> 'Symbicort SMART prolonged the time to first severe exacerbation **(primary variable) vs fixed-dose salmeterol/fluticasone and Symbicort (33% reduction in hazard ratio p=0.003 and 26% reduction in hazard ratio p=0.026, respectively). There were no differences between treatments

in terms of mild exacerbations, lung function, asthma control days*** and asthma-related quality of life. Another secondary endpoint showed **fewer severe exacerbations**** with Symbicort SMART 200/6 µg bd + additional inhalations as needed vs salmeterol/fluticasone 50/250 µg bd + SABA as needed. Rate of severe exacerbation** events per 100 patients every 6 months was 19 for salmeterol/fluticasone + SABA and 12 for Symbicort SMART (p<0.001). The total number of severe exacerbations** was 208 and 125 for salmeterol/fluticasone + SABA and Symbicort SMART, respectively' [referenced to Kuna *et al* (2007)].

The Panel noted with regard to this webpage, the complainant stated that it was not clear what the absolute values were with regard to the claim of 39% reduction in severe exacerbations. The Panel considered that there was no allegation with regard to the prominence of relative risk in relation to absolute risk. The Panel noted AstraZeneca's submission that the absolute figures for the claim in question were stated on the webpage. Based on the very narrow allegation the Panel therefore ruled no breach of Clause 7.2.

Symptom Control

The Panel noted that below the 'Symptom control' title was the statement 'Improvement in asthma control days' [referenced to Kuna *et al* (2007)]. Below this statement, and to the left, was a large red circle with an upwards pointed arrow and the text, '7x more asthma control days vs baseline. Total number of asthma control days was another secondary endpoint'. The '7x' was in much larger font compared to the rest of the text on the webpage. To the right of the red circle in less prominent text it stated:

'Compared with their baseline, patients who received Symbicort SMART 200/6µg bd + additional inhalations as needed had a seven-fold increase in asthma control days (5.8% vs 41.3%). This was similar to the change in asthma control days seen with salmeterol/fluticasone 250µg bd + SABA (5.7% vs 43.7%).'

Below this text was the statement 'p value was not included in paper'.

The Panel noted that Kuna *et al* (2007) was a comparative study of Symbicort SMART versus, *inter alia*, salmeterol/fluticasone. For the secondary outcome variable of asthma-control days, the study authors stated that there was no statistical difference at the 5% level of significance between Symbicort SMART and salmeterol/fluticasone.

The Panel noted the text in the webpage at issue as set out above and considered that it was sufficiently clear that the claim '7x more asthma control days vs baseline' was versus baseline and not versus the comparator arm and ruled no breach of Clause 7.2 and 7.3 in that regard.

The Panel noted that the % of asthma control days at baseline and following treatment were stated for both Symbicort SMART and salmeterol/fluticasone + SABA, with a statement that the result was similar between the two groups. The Panel noted that the claim of 7x more asthma control days was versus baseline and therefore it was not a claim of relative improvement vs a comparator medicine as alleged. The Panel noted its comments above and based on the narrow allegation it considered that the claim at issue was not misleading by virtue of its prominence in this regard and ruled no breach of Clauses 7.2 and 7.3. The Panel therefore ruled no breach of Clause 9.1.

During its consideration of this case the Panel had a number of concerns about the webpages at issue and the completeness of AstraZeneca's response. The Panel provided further detail to AstraZeneca and requested that it be advised of its concerns and asked that the company review the webpages at issue bearing the above points in mind.

Complaint received	**29 October 2018**
Case Completed	**5 July 2019**