CASE AUTH/3585/11/21

COMPLAINANT v ASTRAZENECA

Promotion of Symbicort turbohaler, Trixeo, Bevespi and Daxas

An anonymous contactable complainant who described themselves as a health professional complained about the promotion of Symbicort turbohaler (budesonide/formoterol), Trixeo (formoterol/budesonide/glycopyrronium), Bevespi (glycopyrronium/formoterol) and Daxas (roflumilast).

The complainant stated that he/she had concerns over stretching the boundaries of the Code by AstraZeneca's promotional content on various webpages.

1 The complainant stated that on the Symbicort turbohaler and pMDI devices webpage (https://medicines.astrazeneca.co.uk/home/respiratory/symbicort.html#the-turbohaler-device GB-31536 October 2021) underneath mention of Symbicort pMDI 100/3, dosing was noted as 'Two inhalations in the morning, two inhalations in the evening and two inhalations as needed'. The complainant was concerned that no maximum dosage was stated as indicated in the summary of product characteristics (SPC) for Symbicort 100/3 pMDI device. The way the dosing was written was incorrect as when required usage seemed infinite with no maximum dosage in the way it was presented on the page, which could cause overdosing.

The complainant stated that whether this was dosing for Symbicort in COPD (chronic obstructive pulmonary disease) or asthma was also not presented on the dosing information. The dosing presented on the page without maximum dose qualification and the important advice listed in the SPC as to when medical assessment was needed, was alleged to be in breach of the Code.

2 The complainant stated that the first part of the advertisement on practice nurse website (GB-30263 August 2021) claimed that 'Trixeo offered triple protection for moderate to severe COPD patients from exacerbations, hospitalisations and symptoms'. However, in both the ETHOS study and the KRONOS study, Trixeo showed a non-significant reduction in hospitalisations vs a long-acting beta2 agonist (LABA)/long-acting muscarinic antagonist (LAMA) and inhaled corticosteroid (ICS)/LABA respectively. The complainant stated that as the p-value was non-significant, this should have been made clear on the advertisement and to claim reduction in hospitalisations was a hanging comparison but also not accurate due to the results linking to the p-value non-significance.

3 The complainant alleged that on the Trixeo website homepage (www.trixeo.co.uk), Bevespi was listed at the top of page with the text Bevespi prescribing information. However, no generic name was provided for Bevespi. Every page on the website had the same Bevespi prescribing information text in the same position at the top of the page but no generic name was given considering this was the first and most prominent mention.

The complainant further stated that on the homepage, a statement just above the references read, 'In the clinical trial programme for TRIXEO, LAMA/LABA refers to glycopyrronium/formoterol fumarate and ICS/LABA refers to budesonide/formoterol fumarate'. Budesonide/formoterol was Symbicort (an AstraZeneca medicine), but no prescribing information was provided on the webpage.

4 The complainant stated that on the Trixeo website efficacy webpage (https://www.trixeo.co.uk/home/efficacy.html) results of the trials for Trixeo were presented and Symbicort was mentioned frequently on the webpage as BUD/FOR DPI. No prescribing information was provided on this webpage for Symbicort despite the repeated usage of this medicine mentioned within claims and comparisons in relation to the studies.

5 The complainant stated that Symbicort was mentioned on Trixeo website safety webpage (https://www.trixeo.co.uk/home/safety.html) but, again, no prescribing information was given and further alleged a breach of Clause 2 as there was no prescribing information for Symbicort and no generic name for Bevespi on all the above Trixeo website webpages.

6 The complainant referred to a claim on the Dosing webpage (https://www.trixeo.co.uk/home/dosing.html) that 'AEROSPHERE Delivery Technology enables: 38% to 41% lung deposition with TRIXEO' and alleged that this was misleading as the lung deposition was shown by an in vitro study, which should have been clarified as in vitro data was not the same as patient data and was misleading without clarification.

7 The complainant stated that Eklira (aclidinium bromide) and Daxas (roflumilast) were mentioned on the Learn More webpage (https://www.trixeo.co.uk/home/learn-more.html) but no generic names for either were provided.

The breaking boundaries video on this webpage mentioned Symbicort but, again, no prescribing information was available for the product.

8 Overall

The complainant alleged that the boundaries stretched across these promotional contents brought the industry into disrepute and a breach of Clause 2 was alleged.

The detailed response from AstraZeneca is given below.

1 Symbicort and pMDI devices webpage

In relation to the allegation that it was not clear whether dosing for Symbicort in COPD or asthma was presented in the dosing information, the Panel noted AstraZeneca's submission that the indication for Symbicort Turbohaler and pMDI presentations on the webpage at question was clear at the outset. Whist the Panel noted that the prescribing information for Symbicort in COPD was listed at the top of the page and the footnote that 'Symbicort 100/3 pMDI is to be used in the treatment of Asthma and is not approved in the UK for the treatment of COPD …', as referred to by AstraZeneca, was in very small

font, it noted AstraZeneca's submission that asthma was immediately adjacent to the first mention of Symbicort at the top of the webpage and that in order to navigate to the Symbicort page from the AstraZeneca Medicines website homepage, the visitor must first choose 'Symbicort Asthma' from the 'Respiratory' section; navigating using a direct URL was possible but 'asthma' was mentioned in the URL itself. Further the Panel noted the product information, which referred to the indication for asthma, and that it was not approved in the UK for the treatment of COPD. On balance, the Panel did not consider that the complainant had established that it was not clear whether the dosing statement at issue was in relation to Symbicort in COPD or asthma. The Panel did not consider that the statement at issue was misleading on this narrow point as alleged, no breach of the Code was ruled.

The Panel noted the complainant's allegation that the dosing presented on the page without maximum dose qualification and the important advice listed in the SPC as to when medical assessment was needed was in breach of the Code.

The Panel noted AstraZeneca's submission that it could be reasonably assumed that respiratory health professionals knew that all medications had an upper limit. Moreover, readers could easily access further information about dosing, including maximum dosing if desired as immediately below the statement in question was another statement 'For further information, refer to the Patient Information Leaflet'.

The Panel considered that the webpage at issue was directed broadly at health professionals rather than those who might prescribe in asthma, and it could not be reasonably assumed that every health professional visiting the webpage would be familiar with the dosing in asthma. Whilst the Panel considered that a health professional might not consider that dosing was infinite as alleged it was, nonetheless, important to provide accurate information about dosing, bearing in mind potential patient safety implications. The Panel noted that no upper limit was stated for the dosing of Symbicort and the strong recommendation in the SPC for patients using more than 16 actuations daily to seek medical advice was excluded. Given the strong recommendation in the SPC, the Panel considered that these omissions were such that the information was not sufficiently complete and therefore the statement at issue 'Two inhalations in the morning, two inhalations in the evening and two inhalations as needed' was misleading. A breach of the Code was ruled.

The Panel noted that the claim at issue was referenced to the SPC for Symbicort, however, due to the misleading omissions in relation to the dosing of Symbicort, the Panel did not consider that the claim 'Two inhalations in the morning, two inhalations in the evening and two inhalations as needed' was capable of substantiation and therefore a breach of the Code was ruled.

The Panel noted its comments and rulings above and that it was crucial that health professionals and others could rely completely upon the industry for accurate information about their medicines. The Panel considered that high standards had not been maintained in this regard and a breach of the Code was ruled.

The Panel noted its comments and rulings above. The Panel considered that the provision of accurate information about dosing was important, particularly when the SPC contained warnings such as described above. In these circumstances, and on balance,

the Panel considered that the matter brought discredit upon, or reduced confidence in, the pharmaceutical industry contrary to the requirements of Clause 2 which was used as a sign of particular censure and reserved for such use. A breach of Clause 2 was ruled.

2 Trixeo digital advertisement on practice nurse website for Trixeo

The Trixeo digital advertisement featured 3 frames, with the statement in question on the second frame, stating 'TRIPLE PROTECTION' in bold letters, followed by 'FOR YOUR MODERATE TO SEVERE COPD PATIENTS, FROM EXACERBATIONS, HOSPITALISATIONS AND SYMPTOMS[1]', which was referenced to a paper by Rabe K F *et al*, the ETHOS Study.

The Panel noted that the basis of the complainant's allegation appeared to be that the claim in question was comparative. The complainant cited comparative outcomes in the ETHOS and KRONOS studies stating that Trixeo showed a non-significant reduction in hospitalisations vs a long-acting beta2 agonist (LABA)/long-acting muscarinic antagonist (LAMA) and inhaled corticosteroid (ICS)/LABA respectively. The complainant considered that the non-significant p-value should be made clear in the advertisement.

The Panel noted that the claim at issue referred to 'exacerbations' and 'hospitalisations' separately as two apparently distinct endpoints, and not severe exacerbations which led to hospitalisations as submitted by AstraZeneca.

The Panel noted the complainant's allegation that the reduction in hospitalisations was a hanging comparison.

The Panel noted that while the study, which referenced the claim at issue was comparative, the advertisement and the claim at issue was not, therefore, the Panel did not consider that the complainant had established that the claim 'TRIPLE PROTECTION FOR MODERATE TO SEVERE COPD PATIENTS, FROM EXACERBATIONS, HOSPITALISATIONS AND SYMPTOMS[1]' was a hanging comparison as alleged. No breach of the Code was ruled.

Nor did the Panel consider that the complainant had established that failure to state the p-value rendered the claim misleading or incapable of substantiation as alleged. In the Panel's view, neither the claim in question nor the advertisement were comparative. Based on the very narrow allegation, the Panel ruled no breaches of the Code.

The Panel noted its rulings above and considered that there was no evidence that high standards had not been maintained and no breach of the Code was ruled.

Noting its comments and rulings above, the Panel consequently ruled no breach of Clause 2 of the Code.

3, 4 and 5. Trixeo website Home and Safety and Efficacy webpages

The Panel noted AstraZeneca's submission that the Bevespi prescribing information link on the Trixeo website was the first mention of the brand name and therefore should have included the non-proprietary name immediately adjacent to it and it had not been. Noting

the requirements of the Code in relation to the non-proprietary name and its location, the Panel therefore ruled a breach of the Code as acknowledged by AstraZeneca.

As Symbicort was mentioned on the Trixeo homepage, safety and efficacy webpages, albeit using its non-proprietary name, prescribing information for Symbicort should have been provided as required by the Code. Prescribing information had not been provided and the Panel therefore ruled a breach of the Code in relation to each webpage as acknowledged by AstraZeneca. Nor was there a statement as to where it could be found and the Panel therefore ruled a breach of the Code in relation to each webpage.

The Panel considered that high standards had not been maintained in this regard and a breach of the Code was ruled.

The Panel noted the complainant alleged a breach of Clause 2 because of the lack of Symbicort prescribing information and non-proprietary name for Bevespi on the above webpages. On balance, the Panel considered that the matter was adequately covered by its ruling of a breach of the Code above. The Panel did not consider that the particular circumstances of this case warranted a ruling of a breach of Clause 2 which was a sign of particular censure and was reserved for such use and no breach of the Code was ruled.

6 Trixeo Dosing webpage

The complainant alleged that the webpage was misleading as it was not made clear that the data was from in vitro studies.

The Panel noted AstraZeneca's submission that this claim on the dosing webpage was based on two studies which were both conducted in humans. The relevant footnote indicated that one study was in patients with COPD and the second in healthy male volunteers. The Panel noted that the complainant had made no mention of the footnote and its location. The allegation was limited to what the complainant considered was the in vitro nature of the studies. Noting that the complainant bore the burden of proof, the Panel considered that he/she had not established that the claim was based on in vitro studies as alleged. On this narrow ground, no breaches of the Code were ruled.

The Panel did not consider that there was evidence to show that AstraZeneca had failed to maintain high standards in this regard and no breach of the Code was ruled.

7 Trixeo Learn More webpage

The 'Learn More' webpage was headed 'YOU CAN PREVENT EXACERBATIONS', followed by a banner strip at the top of the page stating 'WEBINARS and FORMULARY PACK'.

Beneath 'WEBINARS' there was a statement: 'These are promotional webinars funded and organised by AstraZeneca, containing both educational and promotional material, intended for UK HCPs only'. This was followed by four video thumbnails of the webinars. Each thumbnail had a brief description of the webinar underneath, followed by links to prescribing information for the medicines mentioned in the webinars.

The Panel noted the complainant's allegation that Eklira and Daxas were mentioned on this webpage but no generic names were provided for these products.

The Panel noted AstraZeneca's submission that as the first mention of the brand names were cited in these links, they should have included the non-proprietary name immediately adjacent to it.

The Panel noted that the non-proprietary names for Eklira and Daxas were not present as required by the Code and it therefore ruled a breach of the Code as acknowledged by AstraZeneca.

The Panel noted that the video titled 'Breaking Boundaries in COPD' was included on the 'Learn More' webpage.

The Panel noted AstraZeneca's submission that the video mentioned Symbicort and could be construed by viewers as promotion of that medicine thus requiring the provision of either embedded prescribing information or a link to it.

The Panel noted the requirements of the Code in relation to prescribing information and its location. Symbicort prescribing information was not provided and the Panel therefore ruled breaches of the Code as acknowledged by AstraZeneca. Nor was there a statement as to where it could be found and the Panel therefore ruled a breach of the Code.

The Panel considered that high standards had not been maintained in this regard and a breach of the Code was ruled.

8 Overall

The Panel noted its comments and rulings above. Whilst the Panel was concerned about the multiple breaches noted above, it, nonetheless, did not consider that the overall circumstances warranted a breach of Clause 2, which was a sign of particular censure and reserved for such use and no breach of Clause 2 was ruled.

An anonymous contactable complainant who described themselves as a health professional complained about the promotion of Symbicort turbohaler (budesonide/formoterol), Trixeo (formoterol/budesonide/glycopyrronium), Bevespi (glycopyrronium/formoterol) and Daxas (roflumilast).

COMPLAINT

The complainant stated that he/she had concerns over stretching the boundaries of the Code by AstraZeneca's promotional content on various webpages.

1 Symbicort turbohaler and pMDI devices (https://medicines.astrazeneca.co.uk/home/respiratory/symbicort.html#the-turbohaler-device GB-31536 October 2021)

The complainant stated that on the webpage underneath mention of Symbicort pMDI 100/3, dosing was noted as 'Two inhalations in the morning, two inhalations in the evening and two inhalations as needed'. The complainant was concerned that no maximum dosage was stated as indicated in the summary of product characteristics (SPC) for Symbicort 100/3 pMDI device. The way the dosing was written was incorrect as when required usage seemed infinite with no maximum dosage in the way it was presented on the page, which could cause overdosing.

The complainant stated that whether this was dosing for Symbicort in COPD (chronic obstructive pulmonary disease) or asthma was also not presented on the dosing information. The complainant noted that the SPC guidance (for asthma) was as follows – Recommended doses: Adults and adolescents (12 years and older): The recommended maintenance dose was four actuations per day, given either as two actuations in the morning and evening or as four actuations in either the morning or evening. For some patients, a maintenance dose of four actuations twice daily might be appropriate. Patients should take two additional actuations as needed in response to symptoms. If symptoms persisted after a few minutes, two additional actuations should be taken. Not more than twelve actuations should be taken on any single occasion. A total daily dose of more than sixteen actuations was not normally needed; however, a total daily dose of up to twenty-four actuations could be used for a limited period. Patients using more than sixteen actuations daily should be strongly recommended to seek medical advice. They should be reassessed, and their maintenance therapy should be reconsidered. The dosing presented on the page without maximum dose qualification and the important advice listed in the SPC as to when medical assessment was needed, was alleged to be in breach of Clauses 6.1, 6.2, 5.1 and 2 of the Code.

2 Trixeo digital advertisement on practice nurse website (GB-30263 August 2021)

The complainant stated that the first part of the advertisement claimed that 'Trixeo offered triple protection for moderate to severe COPD patients from exacerbations, hospitalisations and symptoms'. However, in both the ETHOS study and the KRONOS study, Trixeo showed a non-significant reduction in hospitalisations vs a long-acting beta2 agonist (LABA)/long-acting muscarinic antagonist (LAMA) and inhaled corticosteroid (ICS)/LABA respectively. In ETHOS, 16% reduction vs a LAMA/LABA; p=0.09, in KRONOS 18% reduction vs an ICS/LABA; p=0.2792. As the p-value was non-significant, this should have been made clear on the advertisement and to claim reduction in hospitalisations was a hanging comparison but also not accurate due to the results linking to the p-value non-significance. The complainant alleged that the claim was in breach of Clauses 6.1, 6.2, 5.1 and 2 of the Code.

3 Trixeo website homepage (www.trixeo.co.uk)

The complainant stated that the website seemed to have been approved as one as the same unique identifier and date appeared on every page across the website (GB-29626. DOP: June 2021). The complainant alleged that on the homepage, Bevespi was listed at the top of page with the text Bevespi prescribing information. However, no generic name was provided for Bevespi in breach of Clause 12.3. Every page on the website had the same Bevespi prescribing information text in the same position at the top of the page but no generic name was given considering this was the first and most prominent mention. The complainant further stated that on the homepage, a statement just above the references read, 'In the clinical trial programme for TRIXEO, LAMA/LABA refers to glycopyrronium/formoterol fumarate and ICS/LABA refers to budesonide/formoterol fumarate'. Budesonide/formoterol was Symbicort (an

AstraZeneca medicine), but no prescribing information was provided on the webpage. The complainant alleged a breach of Clauses 12.1, 12.4, 12.6 and 5.1 of the Code.

4 Trixeo website efficacy webpage (https://www.trixeo.co.uk/home/efficacy.html)

The complainant stated that on this webpage, results of the trials for Trixeo were presented and Symbicort was mentioned frequently on the webpage as BUD/FOR DPI. Again, there was no prescribing information provided on this webpage for Symbicort despite the repeated usage of this medicine mentioned within claims and comparisons in relation to the studies. The complainant alleged a breach of Clauses 12.1, 12.4, 12.6 and 5.1 of the Code.

5 Trixeo website safety webpage (https://www.trixeo.co.uk/home/safety.html)

The complainant stated that Symbicort was mentioned on this webpage (ICS/LABA DPI – Budesonide/Formoterol fumarate dihydrate 400/12µg) but, again, no prescribing information was given. The complainant alleged a breach of Clauses 12.1, 12.4, 12.6 and 5.1. The complainant further alleged a breach of Clause 2 as there was no prescribing information for Symbicort and no generic name for Bevespi on all the above Trixeo website webpages.

6 Trixeo webpage (https://www.trixeo.co.uk/home/dosing.html)

The complainant referred to a claim on this webpage that 'AEROSPHERE Delivery Technology enables: 38% to 41% lung deposition with TRIXEO' and alleged that this was misleading as the lung deposition was shown by an *in vitro* study. This should have been clarified as *in vitro* data was not the same as patient data and was misleading without clarification. The complainant alleged a breach of Clauses 6.1, 6.2 and 5.1 of the Code.

7 Trixeo webpage (https://www.trixeo.co.uk/home/learn-more.html)

The complainant stated that Eklira (aclidinium bromide) and Daxas (roflumilast) were mentioned on this webpage but no generic names for either were provided in breach of Clause 12.3.

The breaking boundaries video on this webpage mentioned Symbicort but, again, no prescribing information was available for the product. The complainant alleged breaches of Clauses 12.1, 12.4, 12.6 and 5.1 of the Code.

8 Overall

The complainant alleged that the boundaries stretched across these promotional contents brought the industry into disrepute and a breach of Clause 2 was alleged.

When writing to AstraZeneca, the Authority asked it to consider the requirements of Clauses 6.1, 6.2, 5.1, 2, 12.1, 12.4, 12.6 and 5.1 as cited by the complainant of the 2021 Code. Whilst Clause 12.3 was not specifically referred to in the letter from the case preparation manager, it was cited by the complainant and responded to by AstraZeneca.

RESPONSE

AstraZeneca stated that it was disappointed that despite regular communication and reassurances about ongoing identification of risk and the swift and serious management of

potential issues, the complainant who might be an employee, had decided to approach the PMCPA directly. AstraZeneca stated that it took this complaint very seriously and had carried out a thorough internal investigation to the best of its abilities, with regard to the allegations made. AstraZeneca noted that the signatory who approved the Trixeo website could not be contacted as part of this investigation; AstraZeneca therefore could not fully address why certain decisions were made by him/her.

AstraZeneca noted that the complaint related to three different materials and evidence was not provided by the complainant. Nevertheless, the allegations were noted below together with AstraZeneca's position on each.

COMPLAINT 1

AstraZeneca submitted that the indication for Symbicort Turbohaler and pMDI presentations on the webpage in question was clear at the outset, and that the maximal dosing information in asthma was not required.

In order to navigate to the Symbicort webpage from the AstraZeneca Medicines website homepage (https://medicines.astrazeneca.co.uk/), the visitor must first choose 'Symbicort Asthma' from the 'Respiratory' section. Navigating using a direct URL was possible but it was important to note that 'asthma' was mentioned in the URL itself.

AstraZeneca pointed out that at the top of the webpage next to the first mention of Symbicort was the non-proprietary name **and** the word 'Asthma' immediately adjacent to it making it clear to any visitor accessing the webpage that the content related to Symbicort in asthma.

AstraZeneca submitted that, furthermore, there was a statement immediately underneath the Symbicort pMDI statement in question and graphic that stated 'Symbicort 100/3 pMDI was to be used for the treatment of Asthma....'. This statement, together with the full indication of Symbicort in asthma, further provided unambiguous clarity to all visitors, that the indication for Symbicort was asthma.

AstraZeneca submitted that the statement in question was intended to indicate to readers how the Symbicort pMDI was usually prescribed in asthma as maintenance and reliever therapy (MART) aligned with its licence. It could be reasonably assumed that respiratory health professionals knew that all medications had an upper limit. Moreover, readers could easily access further information about dosing, including maximum dosing if desired, which was clearly provided on the webpage. In fact, immediately below the statement in question was another statement 'For further information, refer to the Patient Information Leaflet'. It was AstraZeneca's view that the statement was clearly not suggesting an 'infinite' number of inhalations, as suggested by the complainant; a reader would reasonably have accessed any of the following documents provided on this webpage to ascertain further dosing information:

- The Symbicort PIL
- The Symbicort pMDI (100/3) SPC details
- The Symbicort (Asthma) Prescribing Information

AstraZeneca refuted breaches of Clauses 6.1, 6.2 and therefore Clauses 5.1 and 2.

COMPLAINT 2

AstraZeneca maintained that the Trixeo statement in the digital advertisement could be substantiated and was not a hanging comparison.

AstraZeneca noted that the licensed indication for Trixeo Aerosphere (AstraZeneca referred to the SPC) was:

> 'A maintenance treatment in adult patients with moderate-to-severe COPD who are not adequately treated by a combination of an ICS and a LABA or combination of a LABA and a LAMA.'

AstraZeneca submitted that this digital advertisement was made up of 3 frames. The statement in question on the second frame could be substantiated within the cited reference – the ETHOS study. The primary endpoint of ETHOS was the annual rate of moderate or severe COPD exacerbations with 'severe exacerbations' defined as those exacerbations leading to hospitalisations or death (and was well recognised by health professionals, learned societies and The National Institute for Health and Care Excellence (NICE) (NICE Guidelines NG115, Last updated: 26 July 2019)).

AstraZeneca submitted that in this study, according to the primary endpoint, Trixeo Aerosphere did significantly reduce the annual rate of moderate or severe COPD exacerbations vs. LABA/LAMA (rate ratio 0.76 (0.69, 0.83); $p<0.001$) and vs. ICS/LABA (rate ratio 0.87 (0.79, 0.95); $p=0.003$). Therefore, the claim that Trixeo provides 'triple protection for your moderate to severe COPD patients from exacerbations, hospitalisations, and symptoms' could be substantiated and was clearly referenced to the ETHOS study.

The statement that 'Trixeo offers protection from exacerbations, hospitalisations and symptoms' was simply a claim, not a comparison, and therefore not a hanging comparison. A comparison would have to include comparative features like 'better', 'reduced' or 'higher' which this claim did not.

AstraZeneca understood that the PMCPA had established that 'presenting data which did not reach statistical significance was not necessarily unacceptable, however, the presentation of such data, including claims, must not be misleading in this regard' (eg Case AUTH/3185/4/19). The intent and impression of this advertisement was clearly not to suggest significance and further to this, the claim could be substantiated by the referenced study.

AstraZeneca refuted breaches of Clauses 6.1, 6.2 and therefore 5.1 and 2.

PART OF COMPLAINTS 3, 5 AND 7

AstraZeneca submitted that throughout the Trixeo website (www.trixeo.co.uk), the complainant alleged the Bevespi prescribing information link was provided but it did not include the generic name despite this being the first and most prominent mention on each webpage. On the 'Learn More' page, Eklira and Daxas were mentioned on this webpage but no generic names for either were provided, therefore the complainant alleged a breach of Clause 12.3.

AstraZeneca noted that the Bevespi, Eklira and Daxas prescribing information links on the Trixeo website should have included the non-proprietary name.

As the first mentions of the brand names were cited in these links, they should have included the non-proprietary name immediately adjacent to it. AstraZeneca believed this was a genuine oversight.

Therefore, AstraZeneca regrettably accepted a breach of Clause 12.3 in this regard.

PART OF COMPLAINTS 3 AND 5, AND COMPLAINT 4

In order to address the remaining allegations and provide clarity, AstraZeneca summarised the salient points for each registration study for Trixeo Aerosphere.

The **ETHOS** study included fixed dose triple combination MDI, Trixeo Aerosphere (budesonide, glycopyrronium, formoterol fumarate [**BGF**]) 320/14.4/9.6 as 160/7.2/4.8mcg, 2 inhalations twice-daily.

The three active comparators were:

1 LABA/LAMA combination MDI, Bevespi Aerosphere (glycopyrrolate, formoterol fumarate [**GFF**]) 14.4/9.6 µg as 7.2/4.8 µg, 2 inhalations twice-daily:
   - Prescribing information for Bevespi Aerosphere was therefore provided.

2 ICS/LABA combination MDI, unlicensed product in same Aerosphere inhaler (budesonide, formoterol fumarate [**BFF**]) 320/9.6µg as 160/4.8µg, 2 inhalations twice-daily:
   - This dosing combination was not available anywhere in the world and so prescribing information for this combination was not available or required as it was not possible to promote it.

3 Fixed dose triple combination, unlicensed product in same Aerosphere inhaler [**BGF]** 160/14.4/9.6 µg as 80/7.2/4.8 µg, two inhalations twice-daily:
   - This comparator was not mentioned in the campaign materials.

The **KRONOS** study included fixed dose triple combination MDI, Trixeo Aerosphere (budesonide, glycopyrronium, formoterol fumarate [**BGF**]) 320/14.4/9.6 as 160/7.2/4.8 µg, 2 inhalations twice-daily.

The three active comparators were:

1 LABA/LAMA combination MDI, Bevespi Aerosphere (glycopyrrolate, formoterol fumarate [**GFF**]) 14.4/9.6 µg as 7.2/4.8 µg as 2 inhalations twice-daily:
   - Prescribing information for Bevespi Aerosphere was therefore provided.

2 ICS/LABA combination MDI, unlicensed product in same Aerosphere inhaler (budesonide, formoterol fumarate [**BFF**]) 320/9.6 µg as 160/4.8 µg 2 inhalations twice-daily:
   - This dosing combination was not available anywhere in the world and so prescribing information for this combination was not available, or required as it was not possible to promote it.

3 ICS/LABA combination DPI, Symbicort Turbohaler (budesonide, formoterol fumarate [BUD/FORM]) 400/12 as 200/6 µg 2 inhalations twice-daily:

- The prescribing information for Symbicort Turbohaler was required where mentioned.

On the homepage, 'Efficacy and Safety' webpages the complainant alleged no Symbicort prescribing information was provided. The complainant alleged breaches of Clauses 5.1, 12.1, 12.4 and 12.6.

AstraZeneca stated that as Symbicort Turbohaler was one of the active comparators in the KRONOS study, on this narrow point, the company accepted breaches of Clauses 12.1 and 12.4. AstraZeneca did not consider that Clause 12.6 was relevant as the omission of providing the link was covered by Clauses 12.1 and 12.4.

As there was no Symbicort prescribing information on the above Trixeo website home, efficacy, and safety webpages, and the lack of non-proprietary name for Bevespi on all of these pages, the complainant alleged a breach of Clause 2.

AstraZeneca stated that given that Bevespi was an active comparator that was licensed and available in the UK, a link to the prescribing information was included on the webpage without a non-proprietary name. AstraZeneca believed this was a genuine oversight but lack of a non-proprietary name posed no potential harm to patients and the circumstances did not warrant a breach of Clause 2.

COMPLAINT 6

AstraZeneca submitted that the claim 'AEROSPHERE Delivery Technology enables: 38% to 41% lung deposition with TRIXEO' could be substantiated and was not misleading.

This claim on the dosing webpage was based on two studies which were both conducted in humans. As the claim could be substantiated and the data was not *in vitro*, this information would not mislead the reader. Therefore, AstraZeneca refuted breaches of Clauses 6.1, 6.2 and therefore 5.1.

PART OF COMPLAINT 7

AstraZeneca accepted that the 'Breaking Boundaries' video should have included Symbicort prescribing information. This video mentioned Symbicort and could be construed by viewers as promotion of that medicine thus requiring the provision of either embedded prescribing information or a link to it. AstraZeneca believed this omission was a genuine oversight.

AstraZeneca stated that it regrettably accepted breaches of Clauses 12.1 and 12.4. AstraZeneca did not consider that Clause 12.6 was relevant as the omission of providing the link was covered by Clauses 12.1 and 12.4. Given that AstraZeneca was unable to provide a certificate to denote confirmation of certification, AstraZeneca accepted a breach of Clause 5.1.

COMPLAINT 8

AstraZeneca noted that the complainant alleged that repeated issues across a number of materials should result in a breach of Clause 2 but submitted that, given it could demonstrate compliance with the Code for the majority of alleged breaches, it fully accepted its mistakes and was committed to correcting these and learning, AstraZeneca refuted a breach of Clause 2.

Summary

AstraZeneca stated that it was disappointed if an external company employee had bypassed the inter-company complaints route or if an internal complainant had bypassed AstraZeneca's whistle-blowing policy to take up the PMCPA's limited time and resources. The accepted breaches were likely due to oversight and were not indicative of widespread poor standards across the company. AstraZeneca submitted that it had a number of policies and training in order to maintain a high level of Code knowledge across the company. AstraZeneca submitted that, in relation to this case, it took immediate corrective action in initiating an internal investigation, temporarily taking down the www.trixeo.co.uk website whilst AstraZeneca performed an internal audit and sought the advice of external Code compliance experts. This demonstrated AstraZeneca's agility and determination to correct the oversights made in the materials at issue in this case and the company's willingness to do the right thing. Affected and other teams had received training in order to update their Code knowledge so that this did not happen again. AstraZeneca took all allegations of non-compliance seriously and always strove to learn from any mistakes made, and implement the knowledge learnt into future practices.

In response to a request for further information, AstraZeneca submitted that it fully accepted its oversight in not including the Symbicort prescribing information on the Trixeo.co.uk website (on the specified pages and in the video referenced) had resulted in the unintentional breach of Clauses 12.1 and 12.4. However, AstraZeneca maintained that robust internal processes existed and that this was an isolated error with additional considerations outlined below, and therefore refuted a breach of Clause 5.1 in this particular instance. AstraZeneca asked the Panel to consider that the website was clearly intended to promote Trixeo and not Symbicort, in fact, there was no mention of the brand name at all and only the class (ICS/LABA) or the generic presentation (BUD/FORM DPI or BFF DPI) was referenced.

What complicated this scenario was that BFF DPI was referenced because it was a comparator in only one of the phase 3 clinical trials for Trixeo, KRONOS. The BFF MDI comparator referenced in ETHOS was not Symbicort, was not commercially available in the UK, and therefore, prescribing information was not required nor available.

Taken together, whilst AstraZeneca accepted that the exclusion of the Symbicort prescribing information had resulted in a technical breach of the Code (Clauses 12.1 and 12.4), it maintained that this breach did not risk misleading clinicians or patient safety. AstraZeneca felt that this did not bring the pharmaceutical industry into disrepute and refuted a breach of Clause 2 of the Code.

PANEL RULING

The Panel noted that the complainant had provided links to the webpages at issue, including the job codes and the date of preparation. The Panel noted, however, that whilst the case preparation manager downloaded and saved pdfs of the webpages from the links provided by the complainant and sent these to AstraZeneca, screenshots of the links were not downloaded, saved and provided to the company. This meant that the pdf copies included the text but not the images or the format as seen by readers of the webpages. AstraZeneca had provided copies of the webpages which contained the corresponding job code and date of preparation and so the Panel made its rulings based on the webpages provided by AstraZeneca.

1 Symbicort and pMDI devices (https://medicines.astrazeneca.co.uk/home/respiratory/symbicort.html#the-turbohaler-device GB-31536 October 2021)

The Panel noted that the webpage in question contained a banner at the top with the prominent title 'Symbicort (budesonide/formoterol)' and referred to 'Asthma' directly below in the same size font. This was followed by a list of links to the SPCs for different strengths and formulations of Symbicort, and a link to prescribing information for Symbicort in Asthma and Symbicort in COPD. Beneath this text was a section headed 'The turbohaler device' followed by 'The Turbohaler device is easy to use' and referred readers to the patient information leaflet for further information followed by images showing the basics of how to use the device. This was followed by a video titled 'Using the Symbicort Turbohaler' above the statement at issue 'Symbicort pMDI 100/3*[4] Two inhalations in the morning, two inhalations in the evening and two inhalations as needed', followed by 'For further information, refer to the Patient Information Leaflet' and further images showing further detail on how to use the device. The asterisk in this claim took readers to a footnote in very small font below the images described above stating 'Symbicort 100/3 pMDI is to be used in the treatment of Asthma and is not approved in the UK for the treatment of COPD. Please note that the alternative strength of Symbicort pMDI is also available (200/6 mcg/inhalation). Symbicort 200/6 pMDI is to be used in the treatment for COPD and is not approved in the UK for the treatment of asthma'.

The Symbicort product information was below the footnote, which included the therapeutic indications for asthma and further stated in normal size font 'Symbicort 100/3 pMDI is to be used in the treatment of asthma and is not approved in the UK for the treatment of COPD'.

In relation to the allegation that it was not clear whether dosing for Symbicort in COPD or asthma was presented in the dosing information, the Panel noted AstraZeneca's submission that the indication for Symbicort Turbohaler and pMDI presentations on the webpage at question was clear at the outset. Whist the Panel noted that the prescribing information for Symbicort in COPD was listed at the top of the page and the footnote that 'Symbicort 100/3 pMDI is to be used in the treatment of Asthma and is not approved in the UK for the treatment of COPD …', as referred to by AstraZeneca, was in very small font, it noted AstraZeneca's submission that asthma was immediately adjacent to the first mention of Symbicort at the top of the webpage and that in order to navigate to the Symbicort page from the AstraZeneca Medicines website homepage, the visitor must first choose 'Symbicort Asthma' from the 'Respiratory' section; navigating using a direct URL was possible but 'asthma' was mentioned in the URL itself. Further the Panel noted the product information, which referred to the indication for asthma, and that it was not approved in the UK for the treatment of COPD. On balance, the Panel did not consider that the complainant had established that it was not clear whether the dosing statement at issue was in relation to Symbicort in COPD or asthma. The Panel did not consider that the statement at issue was misleading on this narrow point as alleged, no breach of Clause 6.1 was ruled.

The Panel noted the complainant's allegation that the dosing presented on the page without maximum dose qualification and the important advice listed in the SPC as to when medical assessment was needed was in breach of the Code. The Panel noted AstraZeneca's submission that the statement in question was intended to indicate to readers how the Symbicort pMDI was usually prescribed in asthma as maintenance and reliever therapy (MART) aligned with its licence. The Panel noted that according to the Symbicort 100/3 SPC, the recommended doses for maintenance and reliever therapy were as follows:

> Adults and adolescents (12 years and older): The recommended maintenance dose is 4 actuations per day, given either as 2 actuations in the morning and evening or as 4 actuations in either the morning or evening. For some patients, a maintenance dose of 4 actuations twice daily may be appropriate. Patients should take 2 additional actuations as needed in response to symptoms. If symptoms persist after a few minutes, 2 additional actuations should be taken. Not more than 12 actuations should be taken on any single occasion.
>
> A total daily dose of more than 16 actuations is not normally needed; however, a total daily dose of up to 24 actuations could be used for a limited period. Patients using more than 16 actuations daily should be strongly recommended to seek medical advice. They should be reassessed, and their maintenance therapy should be reconsidered.

The Panel noted AstraZeneca's submission that it could be reasonably assumed that respiratory health professionals knew that all medications had an upper limit. Moreover, readers could easily access further information about dosing, including maximum dosing if desired as immediately below the statement in question was another statement 'For further information, refer to the Patient Information Leaflet'.

The Panel considered that the webpage at issue was directed broadly at health professionals rather than those who might prescribe in asthma, and it could not be reasonably assumed that every health professional visiting the webpage would be familiar with the dosing in asthma. Whilst the Panel considered that a health professional might not consider that dosing was infinite as alleged it was, nonetheless, important to provide accurate information about dosing, bearing in mind potential patient safety implications. The Panel noted that no upper limit was stated for the dosing of Symbicort and the strong recommendation in the SPC for patients using more than 16 actuations daily to seek medical advice was excluded. Given the strong recommendation in the SPC, the Panel considered that these omissions were such that the information was not sufficiently complete and therefore the statement at issue 'Two inhalations in the morning, two inhalations in the evening and two inhalations as needed' was misleading. A breach of Clause 6.1 was ruled.

The Panel noted that the claim at issue was referenced to the SPC for Symbicort, however, due to the misleading omissions in relation to the dosing of Symbicort, the Panel did not consider that the claim 'Two inhalations in the morning, two inhalations in the evening and two inhalations as needed' was capable of substantiation and therefore a breach of Clause 6.2 was ruled.

The Panel noted its comments and rulings above and that it was crucial that health professionals and others could rely completely upon the industry for accurate information about their medicines. The Panel considered that high standards had not been maintained in this regard and a breach of Clause 5.1 was ruled.

The Panel noted its comments and rulings above. The Panel considered that the provision of accurate information about dosing was important, particularly when the SPC contained warnings such as described above. In these circumstances, and on balance, the Panel considered that the matter brought discredit upon, or reduced confidence in, the pharmaceutical industry contrary to the requirements of Clause 2 which was used as a sign of particular censure and reserved for such use. A breach of Clause 2 was ruled.

2 Trixeo digital advertisement on practice nurse website for Trixeo (GB-30263 August 2021)

The Trixeo digital advertisement featured 3 frames, with the statement in question on the second frame, stating 'TRIPLE PROTECTION' in bold letters, followed by 'FOR YOUR MODERATE TO SEVERE COPD PATIENTS, FROM EXACERBATIONS, HOSPITALISATIONS AND SYMPTOMS[1]', which was referenced to a paper by Rabe K F *et al*, the ETHOS Study.

The Panel noted that the basis of the complainant's allegation appeared to be that the claim in question was comparative. The complainant cited comparative outcomes in the ETHOS and KRONOS studies stating that Trixeo showed a non-significant reduction in hospitalisations vs a long-acting beta2 agonist (LABA)/long-acting muscarinic antagonist (LAMA) and inhaled corticosteroid (ICS)/LABA respectively. The complainant considered that the non-significant p-value should be made clear in the advertisement.

The ETHOS trial assessed two different doses of an inhaled glucocorticoid in fixed-dose triple therapy for COPD. The Panel noted that the primary efficacy endpoint of ETHOS was the annual rate (the estimated mean number per patient per year) of moderate or severe COPD exacerbations. Moderate exacerbations were defined as those leading to treatment with systemic glucocorticoids, antibiotics, or both for at least 3 days; severe exacerbations were defined as those resulting in hospitalization or death. The Panel noted AstraZeneca's submission that in this study, according to the primary endpoint, Trixeo Aerosphere significantly reduced the annual rate of moderate or severe COPD exacerbations vs LABA/LAMA (rate ratio 0.76 (0.69, 0.83); p<0.001) and vs ICS/LABA (rate ratio 0.87 (0.79, 0.95); p=0.003). According to Rabe *et al*, within the secondary and other efficacy analysis, in the non-inferiority analysis of the annual rate of severe exacerbations that was performed in the per-protocol population (all patients with post randomization data obtained before any major protocol deviations), 160-µg–budesonide triple therapy was shown to be non-inferior to budesonide formoterol (rate ratio, 0.82; 95% CI, 0.68 to1.00); however, differences between the 160-µg–budesonide triple-therapy group and either dual-therapy group were not significant.

The Panel noted that the claim at issue referred to 'exacerbations' and 'hospitalisations' separately as two apparently distinct endpoints, and not severe exacerbations which led to hospitalisations as submitted by AstraZeneca.

The Panel noted the complainant's allegation that the reduction in hospitalisations was a hanging comparison. The Panel noted the supplementary information to Clause 6.1 of the Code which stated, *inter alia*, that an area where particular care should be taken by companies was in relation to hanging comparisons, whereby a medicine is described as being better or stronger or suchlike without stating that with which it is compared must not be made.

The Panel noted that while the study, which referenced the claim at issue was comparative, the advertisement and the claim at issue was not, therefore, the Panel did not consider that the complainant had established that the claim 'TRIPLE PROTECTION FOR MODERATE TO SEVERE COPD PATIENTS, FROM EXACERBATIONS, HOSPITALISATIONS AND SYMPTOMS[1]' was a hanging comparison as alleged. No breach of Clause 6.1 was ruled.

Nor did the Panel consider that the complainant had established that failure to state the p-value rendered the claim misleading or incapable of substantiation as alleged. In the Panel's view,

neither the claim in question nor the advertisement were comparative. Based on the very narrow allegation, the Panel ruled no breach of Clauses 6.1 and 6.2.

The Panel noted its rulings above and considered that there was no evidence that high standards had not been maintained and no breach of Clause 5.1 was ruled.

Noting its comments and rulings above, the Panel consequently ruled no breach of Clause 2 of the Code.

3, 4 and 5. Trixeo website Home and Safety and Efficacy webpages

The Panel noted that the Trixeo promotional website was intended for UK health professionals. Each webpage consisted of a banner at the top. On the top right of the banner were links to Trixeo prescribing information and Bevespi prescribing information.

The Panel noted AstraZeneca's submission that the Bevespi prescribing information link on the Trixeo website was the first mention of the brand name and therefore should have included the non-proprietary name immediately adjacent to it and it had not been. Noting the requirements of Clause 12.3 in relation to the non-proprietary name and its location, the Panel therefore ruled a breach of Clause 12.3 as acknowledged by AstraZeneca.

The Trixeo efficacy page was titled 'EFFICACY – TRIXEO DATA' and outlined the ETHOS and KRONOS study designs. It contained a table listing the active comparators in both studies. The KRONOS study included the active comparator ICS/LABA DPI 400/12ug BID.

The Trixeo safety page was titled 'TRIXEO: SAFETY AND TOLERABILITY PROFILE' and contained a table of the most common adverse events, taken from trials of >10,000 patients. The table referenced the KRONOS study in which ICS/LABA DPI 400/12 was one of the comparator arms.

The Panel noted AstraZeneca's submission that Symbicort Turbohaler was an active comparator in the KRONOS study.

The Panel noted the requirements of Clauses 12.1, 12.4 and 12.6 in relation to prescribing information. As Symbicort was mentioned on the Trixeo homepage, safety and efficacy webpages, albeit using its non-proprietary name, prescribing information for Symbicort should have been provided as required by the Code. Prescribing information had not been provided and the Panel therefore ruled a breach of Clauses 12.1 and 12.4 in relation to each webpage as acknowledged by AstraZeneca. Nor was there a statement as to where it could be found and the Panel therefore ruled a breach of Clause 12.6 in relation to each webpage.

The Panel considered that high standards had not been maintained in this regard and a breach of Clause 5.1 was ruled.

The Panel noted the complainant alleged a breach of Clause 2 because of the lack of Symbicort prescribing information and non-proprietary name for Bevespi on the above webpages. On balance, the Panel considered that the matter was adequately covered by its ruling of a breach of Clause 5.1 above. The Panel did not consider that the particular circumstances of this case warranted a ruling of a breach of Clause 2 which was a sign of particular censure and was reserved for such use and no breach of Clause 2 was ruled.

6 Trixeo webpage (https://www.trixeo.co.uk/home/dosing.html)

The Trixeo dosing schedule page had the prominent heading '2 inhalations in the morning + 2 inhalations in the evening' followed by the claim 'TRIXEO COMBINES 3 AGENTS IN 1 DEVICE[1]'. This was followed by the names budesonide (160ug), glycopyrronium (7.2ug) and formoterol (5ug). Underneath was a bold statement 'offer patients a familiar inhaler with next-generation delivery technology[1-3]' followed by the statement at issue '38% to 41% lung deposition with TRIXEO[2,3±]'. The claim was referenced to van den Berge *et al* and Israel S *et al*. The footnote linked to this claim stated 'Lung deposition data are from 2 studies, 1 in patients with COPD and 1 in healthy male volunteers'.

The complainant alleged that the webpage was misleading as it was not made clear that the data was from *in vitro* studies.

The Panel noted AstraZeneca's submission that this claim on the dosing webpage was based on two studies which were both conducted in humans. The relevant footnote indicated that one study was in patients with COPD and the second in healthy male volunteers. The Panel noted that the complainant had made no mention of the footnote and its location. The allegation was limited to what the complainant considered was the *in vitro* nature of the studies. Noting that the complainant bore the burden of proof, the Panel considered that he/she had not established that the claim was based on *in vitro* studies as alleged. On this narrow ground, no breach of Clauses 6.1 and 6.2 were ruled.

The Panel did not consider that there was evidence to show that AstraZeneca had failed to maintain high standards in this regard and no breach of Clause 5.1 was ruled.

7 Trixeo webpage (https://www.trixeo.co.uk/home/learn-more.html)

The 'Learn More' webpage was headed 'YOU CAN PREVENT EXACERBATIONS', followed by a banner strip at the top of the page stating 'WEBINARS and FORMULARY PACK'.

Beneath 'WEBINARS' there was a statement: 'These are promotional webinars funded and organised by AstraZeneca, containing both educational and promotional material, intended for UK HCPs only'. This was followed by four video thumbnails of the webinars. Each thumbnail had a brief description of the webinar underneath, followed by links to prescribing information for the medicines mentioned in the webinars.

The Panel noted the complainant's allegation that Eklira and Daxas were mentioned on this webpage but no generic names were provided for these products.

The Panel noted AstraZeneca's submission that as the first mention of the brand names were cited in these links, they should have included the non-proprietary name immediately adjacent to it.

The Panel noted that the non-proprietary names for Eklira and Daxas were not present as required by the Code and it therefore ruled a breach of Clause 12.3 as acknowledged by AstraZeneca.

The Panel noted that the video titled 'Breaking Boundaries in COPD' was included on the 'Learn More' webpage. The description underneath stated: 'Discover emerging evidence for the use of triple therapy in COPD management. Explore the risks that warrant escalation from dual therapy, as well as the effect of triple therapy beyond exacerbation reduction, and how these factors compare with current treatment guidelines'. Beneath this were the links to Trixeo, Daxas and Bevespi prescribing information.

The Panel noted AstraZeneca's submission that the video mentioned Symbicort and could be construed by viewers as promotion of that medicine thus requiring the provision of either embedded prescribing information or a link to it.

The Panel noted the requirements of Clauses 12.1, 12.4 and 12.6 in relation to prescribing information and its location. Symbicort prescribing information was not provided and the Panel therefore ruled a breach of Clauses 12.1 and 12.4 as acknowledged by AstraZeneca. Nor was there a statement as to where it could be found and the Panel therefore ruled a breach of Clause 12.6.

The Panel considered that high standards had not been maintained in this regard and a breach was Clause 5.1 was ruled.

8 Overall

The Panel noted its comments and rulings above. Whilst the Panel was concerned about the multiple breaches noted above, it, nonetheless, did not consider that the overall circumstances warranted a breach of Clause 2, which was a sign of particular censure and reserved for such use and no breach of Clause 2 was ruled.

Complaint received **27 November 2021**

Case completed **18 January 2023**