CASE AUTH/3683/8/22 *NO BREACH OF THE CODE*

COMPLAINANT v ASTRAZENECA

Allegations about a Trixeo prescribing summary card

CASE SUMMARY

This case was in relation to Trixeo (formoterol fumarate dihydrate, budesonide, glycopyrronium) promotional material on the website of a named publisher.

The Panel ruled no breach of the following Clauses of the 2021 Code in relation to the claim 'Patients who find it difficult to coordinate actuation with inhalation may use Trixeo Aerosphere with a spacer to ensure proper administration of the medicinal product' as the Panel considered that the complainant had not established that this claim was inconsistent with the particulars listed in the Trixeo SPC, nor that it was misleading or incapable of substantiation.

No Breach of Clause 2	**Requirement that activities or materials must not bring discredit upon, or reduce confidence in, the pharmaceutical industry**
No Breach of Clause 5.1	**Requirement to maintain high standards at all times**
No Breach of Clause 6.1	**Requirement that claims must not be misleading**
No Breach of Clause 6.2	**Requirement that claims must be capable of substantiation**
No Breach of Clause 11.2	**Requirement that a medicine must be promoted in accordance with the terms of its marketing authorisation and must not be inconsistent with the particulars listed in its summary of product characteristics**

The Panel ruled no breach of the following Clauses of the 2021 Code in relation to the claim 'Trixeo's innovative Aerosphere technology enables 38% to 41% deposition'. Noting AstraZeneca's submission that all methods used to assess lung deposition were estimates, the Panel considered that the complainant had not established that the intended audience would be misled as alleged, nor that the claim was incapable of substantiation.

No Breach of Clause 2	**Requirement that activities or materials must not bring discredit upon, or reduce confidence in, the pharmaceutical industry**
No Breach of Clause 5.1	**Requirement to maintain high standards at all times**
No Breach of Clause 6.1	**Requirement that claims must not be misleading**
No Breach of Clause 6.2	**Requirement that claims must be capable of substantiation**

The Panel ruled no breach of the following Clauses of the 2021 Code in relation to the allegation that the material omitted Symbicort prescribing information. Noting

AstraZeneca's submission that the formoterol/budesonide MDI dosing combination referred to in the claim at issue was an unlicensed product which was not Symbicort, the Panel considered that the complainant had not established that the material required Symbicort prescribing information.

No Breach of Clause 2	**Requirement that activities or materials must not bring discredit upon, or reduce confidence in, the pharmaceutical industry**
No Breach of Clause 5.1	**Requirement to maintain high standards at all times**
No Breach of Clause 12.1	**Requirement to include up to date prescribing information**

This summary is not intended to be read in isolation.
For full details, please see the full case report below.

FULL CASE REPORT

A complaint was received from an anonymous, contactable complainant, who described themselves as a health professional, and later became non-contactable, about Trixeo (formoterol fumarate dihydrate, budesonide, glycopyrronium) promotional material.

COMPLAINT

The complainant alleged that the prescribing summary card presented for Trixeo by [named publisher] had claims which were untrue. A link to the card in question was provided (GB-37784 Date of preparation: July 2022).

The complainant alleged that the issues were as follows:

1 In the Device section, it was incorporated that patients who found it difficult to coordinate actuation with inhalation may use Trixeo Aerosphere with a spacer to ensure proper administration of the medicinal product. The issue with this claim was that Trixeo was only licensed for use with the Aerochamber spacer and no other spacer. The claim only stated spacer, which implied any spacer use was possible, but this should have been absolutely clear that it was only the Aerochamber spacer that could be used. Considering health professionals were time poor, claims had to be truthful from the outset. The complainant alleged that the claim was in breach of Clauses 6.1, 6.2, 5.1 and 2.

2 Device section – 'Trixeo's innovative Aerosphere technology enables 38% to 41% deposition'. This claim was not transparent as these were estimates only (which was not specified within the claim) and the estimates were based on functional imaging. The complainant alleged that the claim was in breach of Clauses 6.1, 6.2, 5.1 and 2.

3 Clinical evidence section – 'Trixeo Aerosphere reduces symptoms of COPD and improves quality of life vs formoterol/glycopyrronium MDI ($p<0.0001$) and formoterol/budesonide MDI** ($p<0.0001$)'. Formoterol/budesonide was Symbicort, which was an AstraZeneca product but no prescribing information for Symbicort was provided. Only Bevespi and Trixeo prescribing information was given. The complainant alleged that Clauses 12.1, 5.1 and 2 had been breached.

The complainant alleged that patient safety was being put at risk.

When writing to AstraZeneca, the Authority asked it to consider the requirements of Clauses 2, 5.1, 6.1, 6.2 and 12.1 of the Code as cited by the complainant and, in addition, to consider the requirements of Clause 11.2 in relation to Point 1.

RESPONSE

AstraZeneca stated that it would address each of the complainant's allegations according to the relevant clauses of the Code.

Allegation 1: The complainant stated in their letter that 'Trixeo is only licensed for use with the Aerochamber spacer and no other spacer'. The complainant also stated that 'AstraZeneca should have been absolutely clear that it was only the Aerochamber spacer that could be used'. Regrettably, the complainant also questioned AstraZeneca's sensitivity towards the growing pressures in the NHS by stating 'considering healthcare professionals were time poor, claims had to be truthful from the outset' and alleged breaches of Clauses 11.2, 6.1, 6.2, 5.1 and 2.

AstraZeneca submitted that Trixeo Aerosphere was licensed to be used with any spacer. Trixeo Aerosphere was not restricted nor licensed to only be used with the Aerochamber spacer device.

The use of spacer devices to assist patients with difficulty coordinating actuation and inhalation with metered dose inhalers (MDIs) was well established.

The Trixeo Aerosphere Summary of Product Characteristics stated in section 4.2 that *a* spacer may be used to support patient inhalation to ensure proper administration of a medicinal product, the SPC did not restrict or recommend the use with any specific spacer devices: 'Patients who find it difficult to coordinate actuation with inhalation may use Trixeo Aerosphere with a spacer to ensure proper administration of a medicinal product. Compatibility with the Aerochamber Plus Flow-Vu spacer device has been demonstrated (see section 5.2)'.

While the SPC did state that compatibility with the Aerochamber Plus Flow-Vu spacer device had been demonstrated with Trixeo Aerosphere, it did not specifically recommend the use of, nor restrict the use to, the Aerochamber spacer device for administration of the product.

AstraZeneca submitted that this was in contrast to the SPC of other MDIs where recommendations for specific spacer devices had been detailed. AstraZeneca stated that it would provide examples on request if needed.

AstraZeneca submitted:

1 That Trixeo Aerosphere could be used with any suitable spacer. The reference to the Aerochamber device in the SPC was not a recommendation or endorsement of this specific device, rather AstraZeneca had included data from deposition studies conducted with this device to illustrate this was an option.
2 This did not mean, nor did it imply that the Aerochamber device was licensed to be used with, or was the only spacer device that could be used with, Trixeo Aerosphere.
3 Therefore, the reference in the prescribing summary card was factual, accurate, not misleading and capable of substantiation.
4 When treating a patient, a healthcare professional would have the requisite knowledge to understand how and when to use/recommend an appropriate spacer.
5 It followed that patient safety had not been compromised, high standards had been

maintained and the prescribing summary card did not bring discredit to, or reduce confidence in, the industry.

AstraZeneca stated that regarding the complainant's statement 'considering healthcare professionals were time poor, claims had to be truthful from the outset', AstraZeneca completely agreed with this sentiment and that it remained committed to ensuring claims about AstraZeneca's medicines were truthful and balanced.

AstraZeneca therefore strongly refuted breaches of Clauses 11.2, 6.1, 6.2, 5.1 and 2.

Allegation 2: The complainant stated that AstraZeneca was not transparent when stating 'Trixeo's innovative Aerosphere technology enables 38% to 41% deposition'. The complainant stated 'these were estimates only (which was not specified within the claim) and the estimates were based on functional imaging' alleging breaches of Clauses 6.1, 6.2, 5.1 and 2.

AstraZeneca maintained that this claim clearly reflected, and was substantiated by, the available evidence.

AstraZeneca submitted that functional respiratory imaging (FRI) was a well-established method of assessing lung deposition, and the lung deposition range stated in the material clearly reflected the published results from the referenced study. The lung deposition for Trixeo Aerosphere was further supported by additional studies using alternative methods of estimating lung deposition.

AstraZeneca submitted that all methods used to assess lung deposition were estimates, which was widely known and understood amongst health professionals working in the Respiratory field. These data were also consistent with lung deposition data for the dual LABA/LAMA component of Trixeo, Bevespi (glycopyrronium/formoterol fumarate dihydrate) MDI, delivered using Aerosphere technology. AstraZeneca provided a number of references in relation to its statements above.

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

Allegation 3: The complainant referred to this claim in the prescribing summary card when making allegations: 'Trixeo Aerosphere reduces symptoms of COPD and improves quality of life vs formoterol/glycopyrronium MDI ($p<0.0001$) and formoterol/budesonide MDI** ($p<0.0001$)'. The complainant stated that AstraZeneca failed to include prescribing information for Symbicort given formoterol/budesonide MDI was an AstraZeneca product. The complainant noted that Prescribing Information was given for Bevespi (formoterol/glycopyrronium) and Trixeo. The complainant alleged breaches of Clauses 12.1, 5.1 and 2.

The formoterol/budesonide MDI referenced in this claim was not Symbicort and was not marketed in UK. AstraZeneca maintained that prescribing information for this combination was not available, or required, as it was not possible to promote this product in UK.

In order to address this allegation and provide clarity, AstraZeneca had summarised the salient points for the ETHOS 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 160/7.2/4.8 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, 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 marketed 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 strength 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 prescribing summary card.

The allegation referred to comparator arm 2 above, which, as stated above, was not marketed or 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. AstraZeneca referred to the complainant's statement:

> *'Clinical evidence section - Trixeo Aerosphere reduces symptoms of COPD and improves quality of life vs formoterol/glycopyrronium MDI (p<0.0001) and formoterol/budesonide MDI** (p<0.0001).'*

AstraZeneca requested for the Panel to note that the double asterisk (**) after '*formoterol/budesonide MDI**'* referred to a statement on the mentioned material which clearly read '***This regimen is not licensed in the UK'.*

AstraZeneca therefore refuted the alleged breaches of Clauses 12.1, 5.1 and 2 of the Code.

Summary of AstraZeneca's position

AstraZeneca refuted all alleged breaches of this complaint, as outlined above.

AstraZeneca submitted that it subscribed fully to the high ethical and moral spirit of the Code and took its responsibilities under the Code very seriously.

PANEL RULING

The Panel noted that the complaint was in relation to a prescribing summary card on the [named publisher] website titled 'Trixeo® Aerosphere® (formoterol fumarate, glycopyrronium, and budesonide). Text near the top of the webpage included that the prescribing summary card was developed from content provided by AstraZeneca in a format developed by the organisation hosting the material, [named publisher]. AstraZeneca commissioned and funded the development of the prescribing card and 'carried out full medical approval to ensure compliance with regulations'. This text was followed by an adverse event reporting statement, a link to download

the pdf version of the prescribing summary card, and links to Trixeo and Bevespi prescribing information and adverse event reporting information. Underneath was a box containing links to sections headed 'Indication, Dose, Device, Guideline recommendations, Clinical evidence, Safety profile and References'; the information in these links was detailed below the box.

Point 1

The Panel noted that the Device section, which was referenced to the Trixeo SPC, stated 'Patients who find it difficult to coordinate actuation with inhalation may use Trixeo Aerosphere with a spacer to ensure proper administration of the medicinal product'.

The Panel noted that the Trixeo SPC, current at the time of the complaint (date of revision of the text: 1 January 2021), under section 4.2 'Posology and method of administration', included 'Patients who find it difficult to coordinate actuation with inhalation may use Trixeo Aerosphere with a spacer to ensure proper administration of the medicinal product. Compatibility with the Aerochamber Plus Flow-Vu spacer device has been demonstrated (see section 5.2)'.

The Panel noted that the Trixeo SPC section 5.2 'Pharmacokinetic properties', under the subheading 'Effect of a spacer', stated 'The use of this medicinal product with the Aerochamber Plus Flow-Vu spacer in healthy volunteers increased the total systemic exposure (as measured by AUC0-t) to budesonide and glycopyrronium by 33% and 55%, respectively, while exposure to formoterol was unchanged. In patients with good inhalation technique, systemic exposure was not increased with the use of a spacer'.

The Panel noted the complainant's allegation that the claim 'Patients who find it difficult to coordinate actuation with inhalation may use Trixeo Aerosphere with a spacer to ensure proper administration of the medicinal product' implied that any spacer use was possible and was not absolutely clear that it was only the Aerochamber spacer that could be used.

The Panel noted AstraZeneca's submission that Trixeo Aerosphere was licensed to be used with any spacer. Trixeo Aerosphere was not restricted nor licensed to only be used with the Aerochamber spacer device. AstraZeneca further submitted that while the Trixeo SPC did state that compatibility with the Aerochamber Plus Flow-Vu spacer device had been demonstrated, the SPC did not restrict use to that particular spacer device. In this regard, the Panel noted the reference to '**a** spacer' (emphasis added by the Panel) in section 4.2 of the SPC.

Clause 11.2 stated, among other things, that the promotion of a medicine must be in accordance with the terms of its marketing authorisation and must not be inconsistent with the particulars listed in its summary of product characteristics.

Clause 6.1 stated, among other things, that information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must not mislead either directly or by implication and Clause 6.2 required that any information, claim or comparison must be capable of substantiation.

The Panel, noting the information before it, did not consider that the complainant had established that the claim at issue in the Device section was inconsistent with the particulars listed in the Trixeo SPC, nor was it misleading or incapable of substantiation. The Panel therefore ruled **no breach of Clauses 11.2, 6.1 and 6.2** accordingly.

Based on its rulings of no breach above, the Panel subsequently ruled **no breach of Clauses 5.1 and 2**.

Point 2

The Panel noted the complainant's allegation in relation to another claim in the 'Device' section which stated 'Trixeo's innovative Aerosphere technology enables 38% to 41% deposition'; the complainant alleged that this claim was not transparent as these were estimates only (which was not specified within the claim) and the estimates were based on functional imaging.

The Panel noted that Israel *et al* (2020) stated that 'Lung deposition of inhaled therapies can be assessed by several different methods, including pharmacokinetic analysis, functional respiratory imaging (FRI) and gamma scintigraphy'. Israel *et al* explained that 'Pharmacokinetic analysis – assessing concentrations of drug in plasma or urine – can determine general lung deposition, but not specific patterns of distribution within the lung … FRI uses three-dimensional models from computerised tomography scans combined with computational fluid dynamics incorporating drug delivery parameters to calculate aerosol airway deposition and distribution patterns ... Gamma scintigraphy allows assessment of the total lung deposition, regional distribution and extrathoracic (oropharyngeal and stomach) deposition of inhaled drugs …'.

The Panel noted that the lung deposition of Trixeo was assessed by Van den Berge *et al* (2020) using FRI in patients with moderate-to-severe COPD.

Van den Berge stated that deposition as determined by using computational fluid dynamics and formulation characteristics was 38.1% of budesonide, 40.5% of glycopyrrolate and 39.8% of formoterol fumarate. Van den Berge concluded that these results were consistent with scintigraphy findings.

The Panel noted AstraZeneca's submission that all methods used to assess lung deposition were estimates, which was widely known and understood amongst the health professionals working in the Respiratory field.

Whilst the Panel considered that it might have been helpful to provide further details about the study on which the claim 'Trixeo's innovative Aerosphere technology enables 38% to 41% deposition' was based, in the Panel's view, the complainant had not established that the intended audience would be misled on the grounds alleged or that the claim was incapable of substantiation. The Panel ruled **no breach of Clauses 6.1 and 6.2** in this regard.

Based on its rulings of no breach above, the Panel subsequently ruled **no breach of Clauses 5.1 and 2**.

Point 3

The Panel noted that the 'Clinical Evidence' section of the Trixeo prescribing summary card stated 'Trixeo Aerosphere reduces symptoms of COPD and improves quality of life vs formoterol/glycopyrronium MDI ($p<0.0001$) and formoterol/budesonide MDI** ($p<0.0001$)'. A grey box appeared directly below the claim, which contained two footnotes in small font. The double asterisk adjacent to the claim at issue led to the second footnote which stated '**This regimen is not licenced in the UK'.

The Panel noted the complainant's allegation that formoterol/budesonide was Symbicort which was an AstraZeneca product but no prescribing information for Symbicort was provided.

Clause 12.1 stated, among other things, that prescribing information must be provided in a clear and legible manner in all promotional material for a medicine.

The Panel noted that the claim at issue was referenced to Martinez *et al* (2020) and Rabe e*t al* (2020), which both provided data from the ETHOS study. The Panel noted AstraZeneca's submission that the ETHOS study included a fixed dose triple combination MDI, Trixeo Aerosphere, and three active comparators. One of the comparator arms was an ICS/LABA combination MDI, an unlicensed product in the same Aerosphere inhaler (budesonide, formoterol fumarate [BFF]) 320/9.6 µg as 160/4.8µg, 2 inhalations twice-daily. The Panel noted AstraZeneca's submission that this formoterol/budesonide MDI, referenced in the claim at issue, was not Symbicort; this dosing combination was not marketed or available anywhere in the world.

The Panel queried the appropriateness of making a claim against an unlicensed product. Nonetheless, the Panel noted the narrow allegation that Symbicort prescribing information had not been provided.

Noting that the formoterol/budesonide MDI dosing combination referred to in the claim at issue was not Symbicort, the Panel considered that the complainant had not established that the material at issue required Symbicort prescribing information; the Panel ruled **no breach of Clause 12.1** in this regard.

Based on its ruling of no breach above, the Panel subsequently ruled **no breach of Clauses 5.1 and 2**.

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During its consideration of this case, the Panel queried whether comparative claims against an unlicensed product that was not marketed or available anywhere in the world was appropriate. The Panel requested that AstraZeneca be advised of its concerns.

Complaint received **11 August 2022**

Case completed **19 September 2023**