Case AUTH/3709/11/22

HEALTH PROFESSIONAL v ASTRAZENECA

Promotion of Trixeo

CASE SUMMARY

This case was in relation to an advertisement published in Pulse magazine which promoted Trixeo.

The Panel ruled a breach of the following Clauses of the 2021 Code for creating a misleading implication in relation to Trixeo and mortality data that was not capable of substantiation, was not presented objectively and failed to maintain high standards.

Breach of Clause 5.1	**Failing to maintain high standards**
Breach of Clause 6.1	**Making a misleading claim**
Breach of Clause 6.2	**Making an unsubstantiated claim**
Breach of Clause 14.4	**Not encouraging the rational use of the medicine**

The Panel ruled no breach of the following Clause of the 2021 Code on the basis that the advertisement did not imply that Trixeo could prevent deaths.

No Breach of Clause 11.2	**Requirement not to promote a medicine for an unlicensed indication**

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 a complainant who described themselves as a concerned health professional about an advertisement for Trixeo (formoterol fumarate dihydrate/glycopyrronium/budesonide).

COMPLAINT

The complaint related to a Trixeo advertisement which appeared in the October 2022 edition of Pulse magazine. The complainant provided a copy of the advertisement at issue and submitted that, as could be clearly seen at the top of the advertisement, a very strong message regarding exacerbations leading to death could be seen, with [*a statement that*] uncontrolled patients should be started on medication [*sic*].

After reading (and re-reading) a lot of the Phase 3 data, the complainant submitted that the crucial part was that the Phase 3 studies showed no statistical difference in the outcome of

death with the dose in the inhaler in this advertisement – nor with the higher dose; these were also secondary outcomes, not primary outcomes.

The complainant alleged that primary care physicians who looked at this advertisement were likely to link the two statements and think that treating with this triple therapy would lead to less deaths, which was not supported by the Phase 3 data. This was, thus, extremely misleading, and the claims made were not supported by the data. It could easily be taken that, implicitly, there was a claim that this inhaler prevented deaths which was promoting outside of its licence – else why in such a small advertisement give so much space to that exacerbations could lead to death?

When writing to AstraZeneca, the Authority asked it to consider the requirements of Clauses 5.1, 6.1, 6.2, 11.2 and 14.4 of the 2021 Code.

RESPONSE

AstraZeneca submitted that the complaint concerned a Trixeo advertisement in Pulse magazine, October edition.

AstraZeneca submitted that the complaint alleged:

> '*Primary care physicians who look at this advert are likely to link the two statements and think that treating with this triple therapy will lead to less deaths, which is not supported by the phase 3 data. The phase 3 studies showed no statistical difference in the outcome of death with the dose in the inhaler in this advert - nor with the higher dose; these were also secondary outcomes, not primary outcomes.*
>
> *Therefore, it could easily be taken that implicitly there is a claim that this inhaler prevents deaths which is promoting outside of its licence - else why in such a small advert give so much space to that exacerbations can lead to death?*'

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

AstraZeneca's response

AstraZeneca submitted that chronic obstructive pulmonary disease (COPD) remained one of the leading causes of death and emergency admissions in the UK (Snell N, *et al*. 2016; Lane ND, *et al*. 2018). It was well-established and understood by health professionals that COPD patients were at risk of exacerbations and that exacerbations of COPD increased the risk of future exacerbations, hospitalisations, and death (Suissa S, *et al*. 2012). Recently published real world evidence from the UK suggested that even one single moderate exacerbation was associated with an increased risk of hospitalisation and death (Whittaker H, Rubino A, Müllerová H, *et al*. 2022). It was also well recognised that significant clinical inertia existed in the management of COPD in the UK with many exacerbations being under recognised, under reported and under treated (Leidy NK *et al*. 2014; Langsetmo L *et al*. 2008; Xu W *et al*. 2010; Wilkinson TM *et al*. 2004; GOLD 2020 report. 2020).

The first statement in the advertisement 'Just one moderate COPD exacerbation can put your patient in hospital or even cause death' was intended to highlight the risk of serious

consequences that moderate exacerbations could have for patients and the need to ensure patients were optimally controlled to prevent exacerbations. The emphasis of this statement was clearly on exacerbations and the potential impact of them rather than on the risk of death. In addition, the complainant failed to acknowledge that the statement called out the risk of hospitalisation ahead of the risk of death.

The advertisement then positioned Trixeo for COPD patients who were uncontrolled on dual therapy which was aligned with the marketing authorisation and summary of product characteristics (SPC) for Trixeo. In addition, the advertisement clearly stated the licence indication. There was no claim, reference or link to preventing death.

AstraZeneca maintained that the advertisement was clearly highlighting the need to address COPD exacerbations and positioned Trixeo for uncontrolled COPD patients within its indication. There was no claim or reference to Trixeo preventing death, nor was there any undue emphasis on the risk of death in the advertisement.

AstraZeneca therefore refuted a breach of Clauses 5.1, 6.1, 6.2, 11.2 and 14.4 of the ABPI Code of Practice.

PANEL RULING

The Panel noted that the complaint concerned a print advertisement with the prescribing information and adverse event reporting details appearing on the reverse. The advertisement featured a large turquoise central panel which contained the claims at issue starting with the statement 'Just one moderate COPD exacerbation can put your patient in hospital and even cause death', to the right of which was a dragon breathing fire downwards. Below, within the turquoise band was an orange flash with an image of the Trixeo Aerosphere 5 micrograms/7.2 micrograms/160 micrograms and the statements 'For your uncontrolled COPD patients on dual therapy*' and below in a much larger font 'Take action with Trixeo'. Beneath the turquoise band appeared the footnote to the asterisk above, which set out the licensed indication. At the top of the advertisement, above the turquoise band sat the Trixeo brand logo, and the AstraZeneca logo.

The Panel noted the complainant's allegation that health professionals were likely to link the statement regarding exacerbations leading to death and the statement immediately beneath about starting uncontrolled patients on Trixeo and think that treating with the triple therapy would lead to less deaths, which was not supported by the Phase 3 data. The complainant submitted that the Phase 3 studies showed no statistical difference in the outcome of death with the dose displayed in the advertisement in question – nor with the higher dose; these were also secondary outcomes, not primary outcomes.

The Panel noted that Trixeo was licensed as a maintenance treatment in adult patients with moderate to severe COPD who were not adequately treated by a combination of an inhaled corticosteroid and long-acting beta2-agonist or combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist and also that the SPC stated that the recommended and maximum dose was two inhalations twice daily. The Panel noted that although the Trixeo Aerosphere delivered 160mcg of budesonide per inhalation the SPC recommended a dose of two inhalations twice daily that equated to a dose of 320mcg of budesonide twice daily. The Panel noted therefore that the higher dose, 320mcg, used in the Phase 3 ETHOS study (Rabe *et al*, 2020) was consistent with the SPC.

The advertisement appeared in Pulse, a magazine aimed at general practitioners, who the Panel noted were responsible for much of the primary care management of COPD. The Panel noted that references submitted by AstraZeneca indicated that improvement in quality of life, symptom reduction and prevention of exacerbations were key objectives for COPD treatment. In particular, it noted a number of the references submitted including Suissa S, *et al* (2012) supported AstraZeneca's submission that exacerbations were associated with a risk of serious adverse outcomes while Snell N *et al* (2016) and Lane ND, *et al* (2018) confirmed that COPD exacerbations were a leading cause of emergency admissions to hospital. The Panel also noted AstraZeneca's submission that significant clinical inertia existed in the management of COPD with many exacerbations being under recognised, under reported and under treated.

AstraZeneca submitted that the emphasis in the statement 'Just one moderate COPD exacerbation can put your patient in hospital and even cause death' was on exacerbations and the potential impact of them rather than on the risk of death and that it called out the risk of hospitalisation ahead of the risk of death. AstraZeneca maintained that the advertisement highlighted the need to address COPD exacerbations and positioned Trixeo for uncontrolled COPD patients within its indication. The Panel queried AstraZeneca's submission that there was no claim or reference to Trixeo preventing death, nor was there any undue emphasis on the risk of death in the advertisement. The Panel was concerned that AstraZeneca had not commented on the mortality data in the ETHOS trial provided by the complainant, nor had it commented on or provided any data in relation to Trixeo and its effect on exacerbations and mortality.

The Panel noted that the efficacy and safety of Trixeo was evaluated in patients with moderate to very severe COPD in two randomised, parallel group trials, ETHOS and KRONOS.

Details of ETHOS and KRONOS including statistical and non-statistical outcomes appeared in Section 5.1 of the Trixeo SPC which stated that in both studies benefits on exacerbations were observed in patients with moderate, severe and very severe COPD. Outcome data on mortality was not referred to. The Panel noted that the complainant's concern was limited to mortality data.

The ETHOS trial assessed two different doses (320mcg and 160mcg) of an inhaled glucocorticoid in fixed-dose triple therapy for COPD compared to LABA/LAMA and ICS/LABA. 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. The Panel noted that the trial concluded that triple therapy with twice daily budesonide at either the 160mcg or 320mcg dose resulted in a lower rate of moderate or severe COPD exacerbations than glycopyrrolate-formoterol or budesonide-formoterol.

In time to first event analyses performed with the use of the treatment policy estimand in the intention to treat population, the risk of death from any cause in the 320 mcg–budesonide triple-therapy group was 46% lower than that in the glycopyrrolate-formoterol group (28 vs 49 deaths; hazard ratio, 0.54; 95% CI, 0.34-0.87). The Panel noted that the authors of the ETHOS trial concluded that triple therapy with a 320mcg dose of budesonide resulted in a lower all-cause mortality than LAMA-LABA therapy. In addition, the Panel noted the hazard ratio for death from any cause in the 320mcg–budesonide triple-therapy group, as compared with the budesonide-formoterol group was 22% lower (28 vs 34 deaths) but the 95% confidence interval was 0.47 to

1.30 which precluded any definitive conclusion; the Panel noted the wide confidence interval associated with this outcome.

The Panel noted that the advertisement was not comparative, but noted that the licensed indication referred to Trixeo's use in patients who were not adequately treated by a combination of either an inhaled corticosteroid and long-acting beta2-agonist or combination of a long-acting beta2-agonist and a long-acting muscarinic antagonist, the comparators in the ETHOS trial. The Panel considered that the ETHOS trial was thus relevant.

The Panel did not accept, as submitted by AstraZeneca, that the emphasis of the statement 'Just one moderate COPD exacerbation can put your patient in hospital and even cause death' was clearly on exacerbations and the potential impact of them rather than on the risk of death or that, in addition, the complainant had failed to acknowledge that the statement called out the risk of hospitalisation ahead of the risk of death. In the Panel's view, the subject of the sentence was 'one moderate COPD exacerbation', the impact of which was clearly described as both hospitalisation and death. The use of the term 'even' implied that the risk of death was less than the risk of hospitalisation but also gave emphasis to the word 'death'. In the Panel's view, the word 'death' was a term that was particularly likely to catch the reader's eye.

The Panel considered that within a single page printed advertisement that appeared to be an A4 size which contained two clear take-home messages in relation to exacerbations and death, and 'Take action with Trixeo,' some readers were likely to link the two take-home messages. In the Panel's view, some readers would assume that the reason to take action with Trixeo, as referred to in the second take-home message, was because Trixeo would, at the very least, have a positive effect on both the rate of exacerbations and death as referred to immediately above in the first take-home message. The dragon breathing fire in the colour of the turquoise and orange bands, thereby linking the two take-home messages, might be seen as compounding the initial impression. The Panel, noting its comments above, did not agree with AstraZeneca's submission that there was no claim, reference or link to preventing death.

The Panel noted that it was well established that presenting data from secondary endpoints or data which did not reach statistical significance was not necessarily unacceptable, however, the presentation of such data, including claims, must not be misleading. The Panel noted its comments on the ETHOS trial above, including that the hazard ratio for death from any cause in the 320mcg–budesonide triple-therapy group, as compared with the budesonide-formoterol group, was 22% lower (28 vs 34 deaths) but the 95% confidence interval was 0.47 to 1.30 which precluded any definitive conclusion. The Panel noted its comments above about how some readers were likely to interpret the advertisement and link Trixeo to a clear and unambiguous impact on mortality outcomes. Accordingly, the Panel considered that, in the absence of any qualification, the advertisement created a misleading implication in relation to Trixeo and mortality data that was not capable of substantiation and ruled **a breach of Clauses 6.1 and 6.2**.

The Panel noted that there was statistically significant data in relation to the risk of death from any cause in the 320mcg–budesonide triple-therapy group compared to the glycopyrrolate-formoterol group (28 vs 49 deaths; hazard ratio, 0.54; 95% CI, 0.34-0.87). Nonetheless, the Panel noted its comments above and, on balance, considered that, in this regard, high standards had not been maintained and **a breach of Clause 5.1** was ruled.

AstraZeneca had been asked to consider Clause 14.4 which required promotional materials to encourage the rational use of a medicine by presenting it objectively and without exaggerating its properties. Claims should not imply that a medicine has some special merit, quality or property unless this can be substantiated. The Panel noted its comments above in relation to mortality data and Trixeo and considered that the misleading implication in relation to Trixeo and mortality was such that this matter had not been presented objectively. The Panel therefore ruled **a breach of Clause 14.4**.

The Panel noted the complainant's allegation that it could easily be taken that, implicitly, there was a claim that Trixeo prevented deaths which amounted to promoting the medicine outside of its licence contrary to Clause 11.2 of the Code. In the Panel's view, the licensed indication was clear in the advertisement; it appeared in the statement 'For your uncontrolled COPD patients on dual therapy *[4]', 'Take action with Trixeo' and was provided in full albeit in smaller font immediately below the central panel. While the Panel noted its comments above that health professionals were likely to link the two statements, it did not consider that the statements combined implied that Trixeo was licensed to prevent death, rather that a benefit of using Trixeo for its licensed indication, treating COPD patients uncontrolled on dual therapy, was a reduction in the risk of death. This latter point had been dealt with above in relation to Clauses 6.1 and 6.2 of the Code. On balance, the Panel considered that the complainant had not established that the advertisement implied that Trixeo was licensed to prevent deaths, thus promoting Trixeo in a way that was inconsistent with its licence as alleged. In the Panel's view, it was sufficiently clear that Trixeo was used to treat uncontrolled COPD patients and, accordingly, it ruled **no breach of Clause 11.2**.

Complaint received **16 November 2022**

Case completed **20 October 2023**