CASE AUTH/3806/8/23

COMPLAINANT v ASTRAZENECA

Tagrisso (osimertinib) UK product website

CASE SUMMARY

This case was in relation to multiple allegations about AstraZeneca's website for health professionals, Tagrisso Connect. The complainant's allegations concerned three main areas: the availability of and signposting to prescribing information, clarification of whether case studies were real or not, and the presentation of clinical trial data.

The outcome under the 2021 Code was:

Breach of Clause 5.1	**Failing to maintain high standards**
Breach of Clause 12.1	**Failing to include prescribing information**
Breach of Clause 12.6 (x2)	**Failing to include a clear, prominent statement as to where prescribing information could be found**

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 (x4)	**Requirement to maintain high standards at all times**
No Breach of Clause 6.1 (x5)	**Requirement that claims/information/comparisons must be accurate, up to date and not misleading**
No Breach of Clause 6.2 (x3)	**Requirement that claims/information/comparisons must be capable of substantiation**

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 about AstraZeneca was received from an anonymous contactable complainant (who later became non-contactable) who described themselves as a current employee of AstraZeneca.

COMPLAINT

The complaint wording is reproduced below with some typographical errors corrected:

> "I would like to report a complaint with respect to AstraZeneca's UK website for its Lung Cancer Product Tagrisso.

As can be seen from the attached evidence, on entering the website on clicking on the HCP declaration users are directed to a claims page with no access to Prescribing Information (PI).

Going further into the website content users must scroll down four full page frames before getting access to PI, and there is no indication in the first three frames as to where PI can be found.

Additionally, the case studies used in this website do not clarify if they are real case studies or made-up ones.

I believe the lack of access to PI on entry, the lack of indication of where PI can be found demonstrate a failure to maintain high standards, and also breach the code with respect to PI access on website requirements.

Additionally, with the DFS, and CNS DFS claims no P values are provided. There is also no clarity that the CNS DFS endpoint is an exploratory endpoint and NOT a prespecified endpoint. Furthermore, %OS survival rates at 5 years for Tagrisso vs Placebo are also missing. This is an important endpoint in the ADAURA trial.

Specific additional Clauses breached are 5.1, 6.1, and 6.2."

The complainant further added:

> "Just one addition to the clauses already submitted. I feel that 12.6 is relevant here (failing to include a clear, prominent statement as to where PI can be found). Users must scroll down and only on the fourth full screen can see PI for Tagrisso and Gefitinib."

When writing to AstraZeneca, the PMCPA asked it to consider the requirements of Clauses 2, 5.1, 6.1, 6.2, 12.1 and 12.6 of the 2021 Code.

ASTRAZENECA'S RESPONSE

The response from AstraZeneca is reproduced below:

"The complainant's allegations can be broken down as follows:

1. On entering the website, users are directed to claims page with no access to PI. Lack of access to PI on entry, lack of indication of where PI can be found, demonstrate failure to maintain high standards
2. Need to scroll down 4 full page frames before accessing PI. No indication in first 3 full page frames of where PI can be found
3. Not clear if case-studies are real or made-up
4. DFS and CNS DFS claims no P values provided
5. Not clear that CNS DFS endpoint is an exploratory endpoint and not prespecified
6. % of OS survival rates at 5 years for Tagrisso v placebo are missing an important endpoint in ADAURA trial

The Tagrisso Connect website is off-line for previously planned refresh and update.

We will address each of the complainant's allegations according to the relevant clauses of the ABPI.

Allegation 1

On entering the website, users are directed to claims page with no access to PI. Lack of access to PI on entry, lack of indication of where PI can be found, demonstrate failure to maintain high standard

Before entering the Tagrisso Connect website, visitors must self-declare they are a UK HCP. Upon self-declaration a pop-up is immediately shown with the title 'Tagrisso (Osimertinib) is the first and only EGFR-TKI to improve OS and DFS in completely resectable stage II/IIIA EGFR-m NSCLC (ex19del/L858R) vs placebo' and primary endpoint data for DFS is presented and a separate box below this with primary endpoint subset for OS, DFS and DFS CNS (reduction in risk and hazard ratio data displayed also).

Though the pop-up with claims was missing a statement as to where PI could be found via a single click, users are able to exit out of the pop-up and access the prescribing information for Tagrisso at the bottom of all pages of Tagrisso Connect.

We accept a breach of clause 12.6 as the pop-up with claims was missing a statement as to where PI could be found.

We strongly refute the suggestion that we failed to maintain high standards as users are able to exit out of the pop-up box and access the prescribing information for Tagrisso at the bottom of all pages of Tagrisso Connect website which had the statement '*Tagrisso (Osimertinib) prescribing information may be found here*' in a clear and legible manner for both GB and NI. We, therefore, deny a breach of clauses 12.1 and 5.1.

Allegation 2

Need to scroll down 4 full page frames before accessing PI. No indication in first 3 full page frames of where PI can be found

The Tagrisso Connect website has a list of GB and NI prescribing information for Tagrisso with the statement '*Tagrisso (Osimertinib) prescribing information may be found here.*' PI is available upon entry to the website on the main home page and subsequently available in a clear and legible manner at the bottom of all pages of the Tagrisso Connect website. Depending on the size of the screen, the above statement could be seen without scrolling down the page. Even if the screen size is smaller users simply need to scroll down the page to see the above statement and link to the PI.

We strongly refute the suggestion that users would have to scroll 4 full page frames before accessing the PI and therefore deny all alleged breach of clauses including clauses 12.1 and 12.6.

Allegation 3

Not clear if case-studies are real or made-up

Case studies are usually presented from a healthcare professional (HCP), experienced in treating patients with a particular disease, to share their clinical experience, demonstrate clinical considerations and potential outcomes.

The Tagrisso case studies presented are from the experience of the treating HCP and not recommendations from the HCP, they do not replace individual clinical judgement/practice or the summary of product characteristics which sets out the conditions for use of Tagrisso.

The case studies page on the Tagrisso Connect website has a total of 16 Tagrisso case studies covering first line use, adjuvant use, potential severe reactions and warnings, skin toxicity and management of skin toxicity. Each of the 16 case studies were provided by an experienced HCP.

On the Tagrisso Connect website, 10 case studies include a disclaimer that the case study was a real patient. The other 6 case studies included a disclaimer that the case was provided by the presenting HCP from their own clinical experience.

The ABPI Code does not require a disclaimer to be included when presenting case studies to indicate whether the case studies are real patients or made-up.
We strongly refute the suggestion that case studies should indicate if a case study is real or made up and therefore deny all alleged Code breaches.

Allegation 4

DFS and CNS DFS claims no P values provided

The evidence provided by the complainant with the title ‘Tagrisso (Osimertinib) is the first and only EGFR-TKI to improve OS and DFS in completely resectable stage II/IIIA EGFR-m NSCLC (ex19del/L858R) vs placebo’ with primary endpoint data for DFS presented and a separate box below this with primary endpoint subset data for OS, DFS and DFS CNS (reduction in risk and hazard ratio)

The box beneath the DFS and DFS CNS data clearly states, ‘p not provided’ and an asterisk with an explanation underneath.

*Statement reads: Results from the interim analysis released October 2020 showed a statistically significant DFS difference however statistical analyses are not yet available for the 4-year data.

The planned DCO for the primary event-based analysis was February 2022. After the IDMC met in April 2020 and reviewed the data, the committee recommended that the trial be unblinded at a trial level early to complete primary reporting. Due to the unplanned reviews of efficacy for superiority, the alpha allocation had to be revised to control the overall type I error. Based on the recommendation that the trial be unblinded two years early because of evidence of an efficacy benefit and the revision

of the alpha allocation, the data presented at ESMO 2022 with DCO April 11, 2022, is considered an exploratory update. In the exploratory data, there are no reported p-values.

We strongly refute the allegation that DFS and DFS CNS claims require p values to be provided, as this is not a requirement of the ABPI Code, and we therefore deny alleged breaches of clauses 6.1 and 6.2.

Allegation 5

Not clear that CNS DFS endpoint is an exploratory endpoint and not prespecified

The screenshot submitted as evidence by the complainant with the title 'Tagrisso (Osimertinib) is the first and only EGFR-TKI to improve OS and DFS in completely resectable stage II/IIIA EGFR-m NSCLC (ex19del/L858R) vs placebo' with primary endpoint data for DFS presented and a separate box below this with primary endpoint subset data for OS, DFS and DFS CNS (reduction in risk and hazard ratio).

Above the data for the DFS CNS box there is a clear disclaimer which states '*pre-specified exploratory analysis'*

We strongly refute the allegation that it was not clear that DFS CNS endpoint is an exploratory endpoint and not prespecified, and therefore deny alleged breaches of clauses 6.1 and 6.2.

Allegation 6

% of OS survival rates at 5 years for Tagrisso v placebo are missing an important endpoint in ADAURA trial

We note the complainant did not submit any evidence, and it is unclear what part of the Tagrisso Connect website they are referring to.

On the Tagrisso Connect website, on the data page, users can select a tile titled 'ADAURA clinical trial' which will take them to an infographic overview of ADAURA and the 5-year data. The ADAURA clinical trial data page includes the % of OS survival rates at 5 years for Tagrisso v placebo endpoint for ADAURA. The page states:

'In patients with stage II-IIIA disease (primary endpoint subset), the relative reduction in risk, of death was 51%, HR: 0.49, 95.03% CI 0.33 – 0.73; P=0.0004, ARR: 10%.'

We strongly refute the allegation that the % of OS survival rates at 5 years for Tagrisso v placebo an important endpoint in ADAURA was missing and we therefore deny alleged breaches of clauses 6.1 and 6.2.

Summary of AstraZeneca's position

In summary AstraZeneca takes its obligations under the ABPI Code of Practice very seriously and have internal SOPs and processes in place to ensure that we uphold high ethical standard and abide by the ABPI Code. As we have set out above, we

accept a breach of clause 12.6 as the pop-up with claims was missing a statement as to where PI could be found. We vehemently deny bringing the pharmaceutical industry into disrepute, not maintaining high standards and deny being in breach of clauses 2, 5.1, 6.1, 6.2 and 12.1.

AstraZeneca subscribes fully to the high ethical standard and spirit of the ABPI Code of Practice and takes its responsibilities under the code very seriously."

FURTHER INFORMATION FROM ASTRAZENECA

After giving preliminary consideration to the case, the Panel asked AstraZeneca to provide certain references. AstraZeneca provided a number of articles, abstracts and congress presentations and highlighted certain statements within those references which it considered relevant to the allegations.

PANEL RULING

The complaint related to multiple allegations about AstraZeneca's website for health professionals, Tagrisso Connect. The allegations concerned three main areas: prescribing information; case studies; and claims; the Panel considered each in turn.

Prescribing information

The complainant's first allegation was that "on entering the website on clicking on the HCP declaration users are directed to a claims page with no access to prescribing information".

The complainant provided two photographs of the website displayed on a computer screen. The first showed a pop-up by which visitors to the website were informed of the intended audience (UK health professionals) and were required to self-declare whether they were a health professional. Upon clicking the "I am a healthcare professional" tab the user would immediately be presented with Tagrisso claims within a second pop-up. The second photograph provided by the complainant showed part of this second pop-up, which they referred to as a "claims page" and was the subject of the complaint.

The large pop-up in question was titled "Tagrisso® ▼ (osimertinib) is the first and only EGFR-TKI to improve OS and DFS in completely resected Stage II/IIIA EGFRm NSCLC (ex19del/L858R) vs. placebo[1–3]". The Panel noted the following definitions in relation to the claims: EGFR: epidermal growth factor receptor; TKI: tyrosine kinase inhibitor; OS: overall survival; DFS: disease free survival; EGFRm: epidermal growth factor receptor mutation; NSCLC: non-small cell lung cancer; CNS: central nervous system. The pop up contained Tagrisso efficacy and safety data from the ADAURA study and two links which stated "View ADAURA 5-year data infographic here" and "References".

The Panel considered that the pop-up in question contained product claims and was therefore promotional for Tagrisso. The pop-up did not contain prescribing information, either within the text of the pop-up itself or by way of a direct, single click link, or a statement as to where the prescribing information could be found.

The Panel noted AstraZeneca's submission that a user would be able to exit out of the pop-up and access the prescribing information for Tagrisso at the bottom of all pages on the Tagrisso

Connect website. The Panel considered, however, that the large pop-up in question was the first promotional content presented to the user on entry to the website and therefore might be the only content viewed. The Panel therefore considered that the pop-up in question needed to standalone regarding the requirement for prescribing information. Noting that the pop-up did not contain prescribing information, the Panel ruled a **breach of Clause 12.1** of the 2021 Code. The pop-up also did not have a statement as to where prescribing information could be found. The Panel ruled a **breach of Clause 12.6** of the 2021 Code in this regard, as acknowledged by AstraZeneca.

The Panel considered that prescribing information was an important contributor to patient safety. The Panel considered that the absence of prescribing information in the pop-up in question, which was the first, and potentially only, promotional content a user of the Tagrisso website would see, and the absence of a prominent statement in this pop-up as to where prescribing information could be found, was such that AstraZeneca had failed to maintain high standards. The Panel ruled a **breach of Clause 5.1** of the 2021 Code in this regard.

The complainant's second allegation was that "going further into the website content users must scroll down four full page frames before getting access to PI, and there is no indication in the first three frames as to where PI can be found". The complainant had provided a video showing their computer screen where only part of the home page of the website was visible. The Panel noted that the complainant had not provided evidence relating to any other pages of the website; the Panel therefore made its ruling based on the home page of the website only.

The Panel noted that although the video showed that only the top half of the home page was visible within the screen, the video did not demonstrate the user scrolling down four full page frames to access the prescribing information as alleged.

The Panel noted that the amount of the webpage that was visible to a user could be dependent on their screen size, resolution and device type.

AstraZeneca provided a screenshot of the full webpage and submitted that prescribing information for Tagrisso was provided via a link at the bottom of the webpage.

The Panel considered the layout of the home page. The first third of the page (which was visible in the complainant's video) included the page header, tabs to navigate to other sections of the website and the product indication. The second third of the webpage (which was partly visible in the complainant's video) contained three large boxes side by side. These boxes directed the user to other pages of the website: "Data", "Cases" and "Testing". The final third of the webpage included four labelled links to prescribing information (separate Great Britain and Northern Ireland prescribing information links for Tagrisso and for Iressa (gefitinib)) and the adverse event reporting statement.

The Panel took account of AstraZeneca's submission that "…if the screen size is smaller users simply need to scroll down the page…" in relation to viewing the prescribing information statement and link.

Clause 12.6 required that promotional material provided on the internet must include a clear prominent statement as to where the prescribing information can be found. The Panel considered that, irrespective of the device used to view the webpage, it should be clear to the user, without the requirement to scroll, where the prescribing information can be found.

Considering the links to prescribing information were present in the bottom third of the webpage, which for at least some users could not be viewed without scrolling, and there was no statement towards the top of the page informing the user that prescribing information could be found towards the bottom of the page, the Panel ruled a **breach of Clause 12.6** of the 2021 Code.

The Panel considered that there was no evidence to support the complainant's assertion that users would need to scroll "four full page frames" before getting access to prescribing information. The Panel therefore considered that the complainant had not established that AstraZeneca had failed to maintain high standards in this regard and the Panel ruled **no breach of Clause 5.1** of the 2021 Code.

Case studies

The Panel noted the complainant's allegation that the case studies used on the website did not clarify whether they were real or made up. No supporting evidence was provided by the complainant.

The Panel noted AstraZeneca's submission that there were 16 Tagrisso case studies on the website, 10 of which included a disclaimer that the case study was a real patient and six which included a disclaimer that the case was provided by the presenting HCP from their own clinical experience. AstraZeneca did not provide any screenshots of the case studies.

The Panel noted that all complaints were judged on the evidence provided by the parties and that the complainant had the burden of proving their compliant on the balance of probabilities. The Panel considered that the complainant had not established their case on this point. The Panel therefore ruled **no breaches of Clause 6.1 and Clause 6.2** of the 2021 Code in this regard.

Claims

The Panel noted the complainant's allegations that:

- "… with the DFS, and CNS DFS claims no P values are provided"
- "There is also no clarity that the CNS DFS endpoint is an exploratory endpoint and NOT a prespecified endpoint."
- "… %OS survival rates at 5 years for Tagrisso vs placebo are also missing. This is an important endpoint in the ADAURA trial."

The Panel considered that these allegations related to the content of the pop-up referred to above. The Panel considered each allegation in turn.

DFS and CNS DFS claims with no p-values provided

The Panel noted that the ADAURA trial was a double-blind, phase 3 trial investigating osimertinib versus placebo in patients with completely resected EGFR mutation-positive NSCLC. The primary endpoint was disease-free survival (DFS) among patients with stage II to IIIA disease and secondary end points included DFS in the overall population with stage IB to IIIA disease, overall survival (OS), and safety. Assessment of the site or sites of recurrence (including CNS) and the time to CNS disease recurrence or death were prespecified exploratory endpoints. The planned data cut off for the primary event-based analysis was February 2022. The independent monitoring committee recommended that, after review of efficacy data, the trial

be unblinded at a trial level early to complete primary reporting. The data cut off for this unplanned interim analysis was 17 January 2020.

The Panel noted the headline claim “Tagrisso (osimertinib) is the first and only EGFR-TKI to improve OS and DFS in completely resected Stage II/IIIA EGFRm NSCLC (ex19del/L858R) vs. placebo” at the top of the pop-up in question. Primary endpoint (DFS) data at median follow-up of 22.1 months was given directly below and stated, “HR=0.17 (99.06% CI, 0.11-0.26), p<0.001)”. The Panel noted that the data indicated the primary endpoint of the study was met. Below this was a large, highlighted box with prominent bold coloured claims for OS at 60 months, DFS at 48 months and CNS DFS at 48 months in patients with stage II–IIIA disease. Statistical information was stated below each claim, including HR, 95% CI and ARR. For OS at 60 months it stated p=0.0004. For CNS DFS at 48 months it stated “p not provided”. For DFS at 48 months it stated, “p not provided*” and the asterisk led to a footnote which read “*Results from the interim analysis (released October 2020) showed a statistically significant DFS difference, however statistical analyses are not yet available for the 4-year data”.

The Panel noted that the Code did not require the inclusion of statistical information. It required that claims were not misleading and were capable of substantiation; the omission of statistical information was not in itself necessarily misleading. However, material must be sufficiently complete to enable recipients to form their own opinion of the therapeutic value of the medicine. The supplementary information to Clause 6.1 advised that particular care be taken to ensure that there was a sound statistical basis for all claims and comparisons. Differences which did not reach statistical significance must not be presented in such a way as to mislead.

The Panel noted that the DFS data at 48 months was referenced to Tsuboi M, et al. abstract presented at ESMO in 2022, which reported updated exploratory analyses of DFS, after two years added follow up. Data cut off (DCO) was 11 April 2022. The Panel noted AstraZeneca’s submission that based on the recommendation that the trial be unblinded two years early and the revision of the alpha allocation, the data presented at ESMO 2022 with DCO 11 April 2022 was considered an exploratory update and therefore there are no reported p-values.

The Panel considered that it was not necessarily unacceptable to include exploratory data in promotional material, so long as it was presented in such a way as not to mislead the reader. Context was important in this regard.

While the Panel was concerned that the pop-up did not state that the 48-month DFS analysis was considered exploratory, and that the information was presented more prominently than the primary endpoint data, the Panel considered that the complainant’s allegation was very narrow; the complainant only alleged, “no p-value provided”. The Panel noted that directly below the information in question it stated, “p not provided”. It was not for the Panel to infer reasons to support a complainant’s complaint. Based on the very narrow allegation that no p-value was provided, and noting that reference to “p not provided” was stated directly below the information in question, the Panel considered that the complainant had not established that the omission of a p-value *in itself* was misleading and the Panel ruled **no breach of Clauses 6.1 and 6.2** of the 2021 Code on this very narrow point.

The Panel noted the 48-month CNS DFS section was labelled “Pre-specified exploratory analysis”. Text below the CNS DFS data stated, among other things, “p not provided”. The Panel noted AstraZeneca’s submission that this data was considered exploratory and therefore no p-values were presented. While the Panel was concerned that exploratory data was

presented more prominently than primary endpoint data, the Panel considered that the complainant's allegation was very narrow; the complainant only alleged, "no p-value provided". The Panel noted that directly below the information in question it stated, "p not provided". It was not for the Panel to infer reasons to support a complainant's complaint. Based on the very narrow allegation that no p-value was provided, and noting that reference to "p not provided" was stated directly below the information in question, the Panel considered that the complainant had not established that the omission of a p-value *in itself* was misleading, and the Panel therefore ruled **no breach of Clauses 6.1 and 6.2** of the 2021 Code on this very narrow point.

The Panel consequently ruled **no breach of Clause 5.1** of the 2021 Code in relation to the very narrow allegation about p-values.

Description of CNS DFS endpoint

Tsuboi M, et al. (2022) stated that CNS DFS was a pre-specified exploratory endpoint. The Panel took account that "Pre-specified exploratory analysis:" appeared directly above the CNS DFS information. The Panel considered that the complainant had not established that there was "no clarity that the CNS DFS endpoint is an exploratory endpoint and not a prespecified endpoint" as alleged and the Panel ruled **no breach of Clause 6.1** and consequently **no breach of Clause 5.1** of the 2021 Code in this regard.

Percentage OS rates at 5 years for Tagrisso v Placebo

The Panel noted that OS was a key secondary endpoint of the ADAURA trial. The OS hazard ratio at 60 months (HR=0.49), 95.03% confidence interval (0.33–0.73), absolute risk reduction (12%) and p-value (p=0.0004) were all displayed directly below the claim "51% reduction in risk of death" on the pop-up in question. OS rates (85% in the osimertinib group and 73% in the placebo group) were not displayed on the pop-up.

The Panel considered that the complainant had not established that the omission of OS rates on the pop-up created a misleading impression or meant that the pop-up was not sufficiently complete to enable recipients to form their own opinion of the therapeutic value of the medicine. The Panel therefore ruled **no breach of Clause 6.1** of the 2021 Code. The Panel consequently ruled **no breach of Clause 5.1** of the 2021 Code in this regard.

Overall comments

The Panel noted that Clause 2 was a sign of particular censure and reserved for such use. The Panel considered that the matters raised by the complainant were adequately covered by its rulings of the Code above and did not consider that a breach of Clause 2 was warranted. The Panel therefore ruled **no breach of Clause 2** of the 2021 Code.

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During the consideration of this case, the Panel was concerned that claims had been made from exploratory data that was more prominently displayed than the primary endpoint data on the pop-up in question. While the Code did not prohibit the presentation of exploratory analyses in promotional material, great care needed to be taken to avoid creating a misleading impression as to the significance of the results. The Panel requested that AstraZeneca be advised of its concerns in this regard.

Complaint received	**2 August 2023**
Case completed	**28 January 2025**