CASE AUTH/3846/11/23

COMPLAINANT v ASTRAZENECA

Allegations about missing safety information for Calquence

CASE SUMMARY

This case was in relation to an allegation that a promotional leaflet for Calquence (a black triangle product) was misleading by omitting important safety information. Whilst the leaflet stated that no dose adjustment was required for patients with moderate hepatic impairment, the SPC stated that such patients should be closely monitored for signs of toxicity. There was also an allegation that AstraZeneca had breached a previous undertaking in relation to including important safety information.

The outcome under the 2021 Code was:

Breach of Clause 6.1	**Requirement that information must be accurate, up-to-date and not misleading**
Breach of Clause 5.1	**Requirement to maintain high standards at all times**

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 3.3	**Requirement to comply with an undertaking**

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 about AstraZeneca UK Limited.

COMPLAINT

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

> "Subject: Calquence tablet information A Calquence tablet dosing resource (GB-48523 Date of preparation: September 2023) missed out safety information on the need to monitor patients closely for signs of toxicity if the patient had moderate HEPATIC impairment. This was in a section of the resource around hepatic and renal impairment in the dosing guide. The dosing resource was 8 pages long. On page 4 of the resource, the following information was stated, 'No dose adjustment of CALQUENCE is required in patients with mild or moderate renal impairment, mild or moderate hepatic

impairment, or for elderly patients (aged ≥ 65 years)'. The SmPC for Calquence stated the following in section 4.2 > 'However, patients with moderate hepatic impairment should be closely monitored for signs of toxicity'. Calquence is a black triangle product and therefore it is important to provide mandatory information in the resource around monitoring especially as the SMPC called out potential for toxicity. It was also concerning that Astrazeneca had previously had breaches around safety information about other products (AUTH/3618/3/22 - promotion of Forxiga) (but yet again another product was missing important safety information. It would be expected that learnings from cases should always be followed and applied at all times. A link to the dosing resource is: [website link provided]. A link to the SPC is: [website link provided]. 6.1, 5.1, 2 were the clauses that had not been complied with."

When writing to AstraZeneca, the PMCPA asked it to consider the requirements of Clauses 6.1, 5.1 and 2 of the 2021 Code as cited by the complainant and, in addition, Clause 3.3 of the 2021 Code based on the complainant's allegation.

ASTRAZENECA'S RESPONSE

The response from AstraZeneca is reproduced below:

"We write in response to your letter dated 6 November 2023 concerning a complaint from an anonymous complainant who describes themselves as a health professional with respect to allegations about missing safety information for Calquence.

AstraZeneca takes compliance with the ABPI's Code of Practice for the Pharmaceutical Industry (the 'Code') extremely seriously and is committed to maintaining high standards in relation to all information it provides about its products.

AstraZeneca has been asked to consider these allegations with respect to Clauses 6.1, 5.1, 2, and 3.3 of the 2021 Code.

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

1. Missed safety information on the need to monitor patients with moderate hepatic impairment for signs of toxicity.
2. AstraZeneca's previous breaches for missing important safety information for Forxiga (AUTH/3618/3/22) and not following and applying learnings from this case.

Following receipt of this complaint we conducted a review of all our materials to identify if there were other materials missing information around monitoring patients with moderate hepatic impairment for signs of toxicity. Our investigations have revealed that the Calquence tablet dosing resource guide is the only material with this missing information, and this was due to human error. We removed the Calquence tablet dosing resource guide within 24 hours of receiving the complaint from the haematology horizon product website and have also recalled hard copy versions of the guide. We have updated both the digital and hard copy version of Calquence tablet dosing resource guide to include the requirement for close monitoring for signs of toxicity in patients with moderate hepatic impairment.

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

Allegation 1

Missed safety information on the need to monitor patients with moderate hepatic impairment for signs of toxicity.

Calquence tablet doing leaflet is an 8-page material aimed at HCPs to communicate the Calquence dosing instructions, transition from capsules to tablets, highlight key brand benefits beyond dosing particulars, provide information about MyCLL, a patient support programme for Calquence and instructions on how to register.

The title page included Calquence licensed indications, adverse event reporting statement and a statement of where the prescribing information can be found. Page 2 includes information on new formulation transition from capsules to tablets. Page 3 includes information on general dosing and administration and page 4 includes Calquence use in special populations including patients with renal and hepatic impairment, the elderly (aged ≥65 years), cardiovascular disease, and a table on recommended dose modifications of Calquence for grade ≥ 3 adverse reactions. Page 4 also includes the statement '*Please consult the summary of product characteristics (SmPC) for further information on the management of patients receiving Calquence*'.

Page 5 provides information on support programme for patients on Calquence called MyCLL and information on how to sign up for the programme. Pages 6 and 7 include the prescribing information (PI) and page 8 includes key benefit of prescribing Calquence and an overview of safety profile including most common (≥ 20%) any grade adverse drug reactions reported in patients treated with Calquence monotherapy and atrial fibrillation/flutter with a statement for HCPs to '*Please consult the SmPC for further information*'.

Page 4 of the guide states:

The complainant is concerned that additional safety information from section 4.2 of the SmPC which states '*patients with moderate hepatic impairment should be closely monitored for signs of toxicity*' is missing from page 4 of the guide.

The requirement for patients to be monitored in moderate hepatic impairment for signs of toxicity is included clearly within the PI on page 6 under '*hepatic impairment*' heading. There is no requirement in the Code to include all information from the SmPC in the body of a promotional material.

We strive to ensure our materials are of the highest standards and we accept that for completeness, the requirement for monitoring should have been added.

Therefore, we accept a breach of clause 6.1 for missing information on the requirement for close monitoring in patients with moderate hepatic impairment for signs of toxicity.

Allegation 2

AstraZeneca's previous breaches for missing important safety information for Forxiga (AUTH/3618/3/22) and not following and applying learnings from this case.

Case AUTH/3618/3/22 is related to a different product Forxiga, in a different therapy area with different indications and allegations.

The above case is not related to the current complaint which is different and specifically around the requirement for additional monitoring of patients with moderate hepatic impairment. We are committed to ensuring our materials are of high ethical standards and maintain patient safety.

Following the ruling of the above case, employees including signatories, medical and brand teams received training via a webinar. Those that were not able to attend the webinar were assigned the training in our electronic learning platform. The case was also covered in our monthly case summaries provided by our 3rd party training provider. Learning from the case was also shared via email.

We therefore strongly refute and deny a breach of clause 3.3 and are fully compliant with the undertaking given with respect to case AUTH/3618/3/22.

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 6.1 for missing information on the requirement to closely monitor patients with moderate hepatic impairment for signs of toxicity. Our investigations have revealed that the Calquence tablet dosing resource guide is the only material with this missing information, and this was due to human error. We removed the Calquence tablet dosing resource guide within 24 hours of receiving the complaint from the haematology horizon product website and have also recalled hard copy versions. We have updated both the digital and hard copy version of Calquence tablet dosing resource guide to include the requirement to closely monitor patients with moderate hepatic impairment for signs of toxicity. We vehemently deny bringing the pharmaceutical industry into disrepute, not maintaining high standards and breach of an undertaking and deny being in breach of clauses 2, 5.1 and 3.3.

AstraZeneca subscribes fully to high ethical standards, abides by the spirit of the ABPI Code of Practice and takes its responsibilities under the Code very seriously."

PANEL RULING

The Panel noted the eight-page digital leaflet at issue was titled "HOW TO DOSE CALQUENCE (acalabrutinib) TABLETS". The first section of the leaflet was titled "NEW FORMULATION, SAME CONFIDENCE" with the subtitle "CALQUENCE (acalabrutinib) IS NOW PROVIDED IN TABLET FORM". The page informed readers that Calquence tablets were being introduced to the market in August 2023 and that Calquence capsules were scheduled to be phased out by December 2023. The page included information on bioequivalence, dosing schedule, posology, details on co-administration with acid-reducing agents and provided information which would be required to update pharmacy systems, patient prescriptions and records.

The second section was titled “DOSING AND ADMINISTRATION FOR CALQUENCE TALETS” and described the posology and method of administration, including in special populations, and recommended dose modifications for grade ≥ 3 adverse reactions. The Panel acknowledged the wording on page 4 of the leaflet, as quoted by the complainant, which said “No dose adjustment of CALQUENCE is required in patients with mild or moderate renal impairment, mild or moderate hepatic impairment, or for elderly patients (aged ≥ 65 years)”. At the bottom of the page, in smaller font was the statement “Please consult the SmPC for further information on the management of patients receiving CALQUENCE”.

The third section of the leaflet was titled “SUPPORT FOR CALQUENCE PATIENTS”. It included information on the MyCLL patient support programme for patients prescribed Calquence. This was followed by the prescribing information. The final section of the leaflet was titled “CHOOSE CALQUENCE FOR YOUR ELIGIBLE PATIENTS WITH CLL”. This section was one page long and included efficacy and safety information and references.

Allegation 1 – missing safety information (Clause 6.1)

The Panel noted Calquence (acalabrutinib) was indicated as:

- Monotherapy or in combination with Obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)
- Monotherapy for the treatment of adult patients with CLL who have received at least one prior therapy.

Section 4.2 of the summary of product characteristics (SPC) required that treatment with Calquence was initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Section 5.2 of the SPC stated Calquence was metabolised in the liver.

The complainant alleged the leaflet was incomplete as it missed out important safety information on the need to monitor patients closely for signs of toxicity if the patient has moderate hepatic impairment. This Panel noted that this was important because Calquence was metabolised in the liver and was a black triangle drug.

The Panel noted section 4.2 of the SmPC, special populations, stated:

> “No dose adjustment is recommended in patients with mild or moderate hepatic impairment (Child-Pugh A, Child-Pugh B, or total bilirubin between 1.5-3 times the upper limit of normal [ULN] and any AST). However, patients with moderate hepatic impairment should be closely monitored for signs of toxicity. It is not recommended to use Calquence in patients with severe hepatic impairment (Child-Pugh C or total bilirubin >3-times ULN and any AST).”

Clause 6.1 required, among other things, that claims must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis and material must be sufficiently complete to enable recipients to form their own opinion of the therapeutic value of the medicine.

The Panel noted Astra Zeneca's submission that the leaflet was aimed at health professionals to communicate the Calquence dosing instructions, transition from capsules to tablets, highlight key brand benefits beyond dosing particulars and provide information about a patient support programme. Although AstraZeneca did not comment on how the leaflet was distributed, the Panel noted, from the certificate provided by AstraZeneca, that the material was described as a leave piece. Page 4 of the leaflet stated "No dose adjustment of CALQUENCE is required in patients with mild or moderate renal impairment, mild or moderate hepatic impairment, or for elderly patients (aged ≥ 65 years)".

The Panel considered the immediate and overall impression of the dosing section of the leaflet. The Panel noted that the primary purpose of the material was to introduce the new tablet formulation and facilitate transition of patients from capsule formulation. In the Panel's view health professionals could be misled into thinking monitoring for signs of toxicity in patients with moderate hepatic impairment was no longer required for the tablet formulation. A statement directing them to the SPC when prescribing was not sufficient, particularly when the need for close monitoring of those with moderate hepatic impairment was a very important caveat to the fact that no dose adjustment was required for such patients. Notwithstanding that Calquence prescribers were experienced specialists in the field of cancer treatment, in the Panel's view, the leaflet was not sufficiently complete and ruled **a breach of Clause 6.1**, as acknowledged by AstraZeneca.

Allegation 2 – failure to comply with an undertaking (Clause 3.3)

The complainant alleged that AstraZeneca had failed to apply learnings regarding missing important safety information from a previous case (Case AUTH/3618/3/22).

The Panel noted that Case AUTH/3618/3/22 related to a different product, Forxiga, which was indicated in a different therapy area. This case concerned a misleading claim as dosing information for patients with severe hepatic impairment was placed in a footnote, rather than missing the requirement for additional monitoring of patients with moderate hepatic impairment. Whilst there was a similarity, the Panel did not consider the cases to be sufficiently similar such that AstraZeneca could be ruled in breach of the undertaking provided in the previous case. The Panel therefore ruled **no breach of Clause 3.3**.

Clause 5.1

The Panel took account of AstraZeneca's submission that an internal investigation revealed the "how to dose Calquence tablets" leaflet was the only material with the missing information, and they had put corrective and preventative measures in place. However, the Panel considered the fact that Calquence was a black triangle product, and that the omission of information related to patient safety and in a way that conflicted with the SPC, demonstrated that AstraZeneca had failed to maintain high standards in this case. The Panel ruled **a breach of Clause 5.1**.

Clause 2

Clause 2 was a sign of particular censure and was reserved for such use. The Panel recognised that AstraZeneca had conducted an investigation in response to this complaint and there were no other materials with this information missing. The information had been missed due to human error and AstraZeneca had put corrective and preventative measures in place. The Panel considered that the matters raised in this complaint were adequately covered by its

rulings and breaches 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**.

Complaint received **03 November 2023**

Case completed **28 November 2024**