CASE AUTH/3782/6/23 ***NO BREACH OF THE CODE***

COMPLAINANT v ASTRAZENECA

Alleged misleading information on AstraZeneca's Forxiga webpage

CASE SUMMARY

This case was in relation to the 'Prescribing and Dosing' webpage of the Forxiga (dapagliflozin) promotional website. The complainant alleged that the webpage was misleading with regard to information presented on Forxiga's renal considerations.

The outcome under the 2021 Code was:

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 information must be accurate, up-to-date and not misleading**
No Breach of Clause 6.2	**Requirement that information/claims/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 was received about AstraZeneca UK Limited from an anonymous complainant who described themselves as a health professional.

COMPLAINT

The complainant alleged that information presented on renal considerations around Forxiga on a Forxiga promotional website did not present any information on moderate renal impairment, despite this information being documented in the renal section (section 4.4) of the summary of product characteristics (SPC) of Forxiga. The SPC information listed the following critical information – 'In patients with moderate renal impairment (eGFR < 60 mL/min/1.73m^2), a higher proportion of patients treated with dapagliflozin had adverse reactions of increase in parathyroid hormone (PTH) and hypotension, compared with placebo'. The complainant provided a link to the promotional webpage (website link provided) which they described as 'misleading'. On this webpage, towards the bottom of the page there was a section titled 'What renal considerations are there with FORXIGA?'. The complainant alleged that the information in the section around renal impairment did not mention the 'critical SPC information' in relevance to moderate renal impairment. The complainant alleged this was a patient safety risk as a prescriber should always have the full information to hand rather than the cherry-picked information about renal impairment with no mention on the page that in patients with moderate renal impairment (eGFR

< 60 mL/min/1.73m^2), a higher proportion of patients treated with dapagliflozin had adverse reactions of increase in parathyroid hormone (PTH) and hypotension, compared with placebo. The complainant alleged breaches of Clauses 6.1, 6.2, 5.1 and 2 of the Code. They stated that AstraZeneca had recently had numerous Code breaches which included Clause 2 rulings, so it was concerning to them that moderate renal considerations information which was crucial to patient safety had not been included in a section which was about all considerations around renal impairment. The complainant stated that a proactive approach to Code compliance was absolutely crucial especially considering the exposure of these messages to health professionals.

When writing to AstraZeneca, the PMCPA asked it to consider the requirements of Clauses 6.1, 6.2, 5.1 and 2 of the 2021 Code as cited by the complainant.

RESPONSE

AstraZeneca submitted that it took compliance with the Code extremely seriously and was committed to maintaining high standards in relation to all information it provided about its products and in all related activities.

AstraZeneca had been asked by the PMCPA to consider these allegations in respect to Clauses 2, 5.1, 6.1 and 6.2 of the Code.

The complaint

AstraZeneca summarised the complainant's allegations as follows:

1 Forxiga (dapagliflozin) promotional website 'Prescribing and Dosing' page was misleading.

The complainant alleged that the 'Prescribing and Dosing' page was misleading by not including '*any* information on moderate renal impairment'. The complainant alleged that information documented in section 4.4 of the dapagliflozin SPC regarding patients with moderate renal impairment (eGFR < 60 mL/min/1.73m^2) was '*critical*' information that was missing.

2 Safety information was *'cherry-picked'* putting patient safety at risk.

The complainant alleged that AstraZeneca had '*cherry-picked*' and therefore omitted '*critical*' safety information presented in the section entitled 'What renal considerations are there with FORXIGA?', in the Prescribing section of the website, by not including an increase in parathyroid hormone (PTH) and hypotension seen in moderate renal impairment. The complainant alleged that this was a patient safety risk as a prescriber should always have the full information to hand.

AstraZeneca's response to these allegations sought to establish that:

- The renal considerations subsection of the prescribing and dosing part of the website was in keeping with the licence for dapagliflozin and was accurate, balanced, and fair. According to the SPC, dapagliflozin did not require any dose adjustment, nor specific monitoring, for patients with moderate renal impairment.
- There was clear direction to individuals at the top of every website page to prescribing information (PI) as well as links from the 'Prescribing and Dosing' to the 'Safety' page,

where there was a link to refer to the SPC for further information. The PI clearly stated at the top 'Consult Summary of Product Characteristics before prescribing'.
- AstraZeneca considered that the information to support responsible prescribing of dapagliflozin, including the clinical considerations for prescribing, safety, and adverse events, were included in its promotional material.

AstraZeneca addressed each of the complainant's allegations according to the relevant clauses of the Code. AstraZeneca provided a PDF copy of the relevant pages of the Forxiga website.

AstraZeneca's response to the allegations

Background information about the website

The Forxiga website was owned by AstraZeneca and was designed to provide information about Forxiga (dapagliflozin) to health professionals in Great Britain.

Clause 6.1

The complainant alleged *'Information presented on renal considerations around Forxiga on a Forxiga promotional website did not present **any** information on moderate renal impairment, despite this information being documented in the renal section (section 4.4) of the SPC of Forxiga'.* The complainant went on to allege that *'the information in the section around renal impairment did not mention the **critical** SPC information in relevance to moderate renal impairment'.*

AstraZeneca stated that dapagliflozin was licensed for use in adults for the treatment of chronic kidney disease and could be initiated from an eGFR as low as 15ml/min per 1.73m^2 which included people with moderate renal impairment, which was defined as eGFR 30–59ml/min per 1.73m^2.

Within the 'Renal Considerations' section, which was a subset of the 'Prescribing and Dosing' page of the website, AstraZeneca submitted that there were numerous statements which therefore applied to people with moderate renal impairment (eGFR 30–59 ml/min per 1.73m^2), namely:

'- *Dose adjustments are not required based on renal function*
- *For cardiorenal protection, can initiate in patients with eGFR ≥15 mL/min/1.73 m²*
- *Consider additional glucose lowering treatment in patients with T2D with eGFR <45 mL/min/1.73 m², as glycaemic efficacy of FORXIGA is reduced*
- *In patients with severe renal impairment, the glucose lowering effect of FORXIGA is likely absent*
- *Cardiorenal protective effects are maintained in patients with eGFR <45 mL/min/1.73 m².*'

AstraZeneca submitted that, consequently, the complainant's position that the '…promotional website did not present ***any*** information on moderate renal impairment…' was not correct and therefore AstraZeneca denied a breach of Clause 6.1.

AstraZeneca stated that the 'Prescribing and Dosing' section of the website, that was the focus of this complaint, related to prescribing and dosing in people with renal impairment. This section aimed to provide health professionals with an overview of pertinent information to support the

practicalities of prescribing, and specifically to clearly inform about dosing in renal impairment. AstraZeneca submitted that the SPC did not require any dose adjustment, nor change in monitoring, nor considerations regarding patient selection of people with moderate renal impairment and prescribing of dapagliflozin. The SPC included the information around PTH and hypotension in the special warnings section. However, neither of these impacted how a health professional would dose dapagliflozin and therefore, AstraZeneca submitted, they need not be placed in a prescribing and dosing section. Furthermore, the Code did not mandate reproduction of the entire SPC in promotional material. Neither increases in PTH nor hypotension, *per se*, were listed within the SPC as adverse events. AstraZeneca submitted that the information the complainant had highlighted was therefore not 'critical' information to the patient selection or dosing of renal of dapagliflozin [sic] and therefore AstraZeneca denied a breach of Clause 6.1.

AstraZeneca submitted that the website clearly and prominently stated in the chronic kidney disease (CKD) section *'FORXIGA was generally well tolerated in the study population, consistent with the known safety profile of FORXIGA¹. Please refer to the Summary of Product Characteristics for a full list of Adverse Events'.* There was also a separate, dedicated section on the website regarding hypotension and hypovolemia, on the same webpage as the *'Prescribing and Dosing – What renal considerations are there with FORXIGA?'*. This section separately identified scenarios that could result in hypotension in all patients receiving dapagliflozin as per the SPC and represented a broader population than the moderate renal impairment population alone, including the elderly, people on diuretics and anti-hypertensives. AstraZeneca submitted that all information pertaining to safe prescribing and dosing in any population, including those with moderate renal impairment, had been included and had not been 'cherry-picked'.

In conclusion, AstraZeneca submitted that the section around 'Renal Considerations' appropriately covered dosing information with respect to all individuals with renal impairment, including those with moderate renal impairment. The website provided clear links to the SPC. Further, AstraZeneca believed it had reflected the evidence clearly, had not misled by omission, and that the material was sufficiently complete to enable the reader to form their opinion and accordingly, therefore, it did not consider there had been a breach of Clause 6.1.

Clause 6.2

AstraZeneca submitted that the complainant had raised no concerns regarding claims or comparisons made. As such, AstraZeneca maintained that all claims remained capable of substantiation and were fully aligned to the SPC, and therefore denied a breach of Clause 6.2.

Clause 5.1 of the Code

AstraZeneca maintained that high standards were upheld at all times. AstraZeneca refuted the allegation that there had been a breach of Clause 5.1.

Clause 2 of the Code

AstraZeneca stated that it strongly believed that its actions in this matter had not brought discredit to, or reduced confidence in, the pharmaceutical industry and so did not constitute a breach of Clause 2 of the Code.

AstraZeneca submitted that prescribing information, inclusive of those with moderate renal impairment, had been included within the renal considerations section of the prescribing and dosing webpage. No critical information regarding dosing or prescribing in the moderate renal impairment population had been omitted or cherry-picked, given no change in: dose, patient selection or monitoring for this specific population was required by the SPC. There was, therefore, no evidence that patient safety was jeopardised by the website. AstraZeneca strongly denied any allegation of a breach of Clause 2.

Summary of AstraZeneca's position

In conclusion, AstraZeneca stated it took compliance with the Code extremely seriously and was committed to maintaining high standards in relation to all information it provided about its products and in complying with the Code. AstraZeneca was confident that the information provided above showed that the claim was consistent with the SPC and provided sufficient information and context for the health professional to make an informed prescribing decision for their patients, and was not misleading. Finally, for the reasons provided above, AstraZeneca refuted all allegations by the complainant, specifically breaches of Clauses 2, 5.1, 6.1 and 6.2 of the Code.

PANEL RULING

The Panel noted that the complainant had provided a link to a Prescribing and Dosing webpage on the Forxiga (dapagliflozin) promotional website and alleged that the webpage was misleading with regard to information presented on Forxiga's renal considerations. Whilst AstraZeneca's submission in response to the complaint referred to other pages of the Forxiga website, the Panel considered that the complainant's allegations in relation to the website were based on the Prescribing and Dosing webpage and therefore made its rulings on that webpage accordingly.

The Panel noted that the header of the Prescribing and Dosing webpage at issue contained the dropdown menu headings 'Chronic Kidney Disease', 'Type 2 Diabetes', 'Heart Failure', 'About FORXIGA', 'Resources' and 'Contact'.

Beneath the header was a section with a large 'hero image' and the bold heading 'Prescribing & Dosing', with a description of Forxiga and its indication. The next section of the webpage was titled 'Learn more about how to prescribe FORXIGA (dapagliflozin) in patients living with T2D, heart failure (HF), or CKD'. Below this was a section titled 'Detailed overview of indications' which contained various expandable sections which answered questions including 'What renal considerations are there with FORXIGA?' and 'Who is at risk of volume depletion and hypotension?'. Other questions were related to liver impairment, type 1 diabetes and diabetic ketoacidosis.

The Panel noted that the section titled 'What renal considerations are there with FORXIGA?' stated:

'
- Dose adjustments are not required based on renal function
- For cardiorenal protection, can initiate in patients with eGFR ≥15 mL/min/1.73 m²
- Consider additional glucose lowering treatment in patients with T2D with eGFR <45 mL/min/1.73 m², as glycaemic efficacy of FORXIGA is reduced

  - In patients with severe renal impairment, the glucose lowering effect of FORXIGA is likely absent
  - Cardiorenal protective effects are maintained in patients with eGFR <45 mL/min/1.73 m²
- It is not recommended to initiate treatment with dapagliflozin in patients with eGFR <15 mL/min/1.73 m².'

The section titled 'Who is at risk of volume depletion and hypotension?' listed the types of patients at risk, including those listed in the Forxiga SPC Section 4.4, Special warnings and precautions for use, such as patients on anti-hypertensive therapy with a history of hypotension or elderly patients.

The Panel noted the complainant's allegation that the information in the section titled, 'What renal considerations are there with FORXIGA?' did not mention 'the critical SPC information in relevance to moderate renal impairment'. The critical information not mentioned on the webpage appeared to be that in patients with moderate renal impairment (eGFR < 60 mL/min/1.73m^2), a higher proportion of patients treated with dapagliflozin had adverse reactions of increase in parathyroid hormone (PTH) and hypotension, compared with placebo. In this regard, the Panel noted the complainant's allegation that information about renal impairment had been 'cherry picked' and that the 'prescriber should always have the full information'.

With regard to renal considerations, the Panel noted the following information from the Forxiga SPC:

> Section 4.2, Posology and method of administration, Posology, Special populations, Renal impairment, stated that no dose adjustment was required based on renal function.
>
> Section 4.3, Contraindications, did not list any contraindications in relation to renal impairment.
>
> Section 4.4, Special warnings and precautions for use, Renal impairment, stated 'In patients with moderate renal impairment (eGFR < 60 mL/min/1.73 m^2), a higher proportion of patients treated with dapagliflozin had adverse reactions of increase in parathyroid hormone (PTH) and hypotension, compared with placebo.
>
> Section 4.8, Undesirable effects, listed volume depletion as an Uncommon (≥ 1/1,000 to < 1/100) adverse reaction, with a footnote stating 'Volume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia, hypotension.' There was no adverse reaction listed in relation to increase in parathyroid hormone.
>
> Section 4.9, Overdose, stated 'Rates of adverse events including dehydration or hypotension were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters, including serum electrolytes and biomarkers of renal function.

The Panel noted AstraZeneca's submission that there was a dedicated section on the Prescribing and Dosing webpage regarding hypotension and hypovolemia, which separately identified scenarios that could result in hypotension and represented a broader population than the moderate renal impairment population alone, including the elderly and people on diuretics or anti-hypertensives.

The Panel noted AstraZeneca's submission that dapagliflozin was licensed for use in adults for the treatment of chronic kidney disease and could be initiated from an eGFR as low as 15 ml/min per 1.73 m^2 which included people with moderate renal impairment. AstraZeneca submitted that neither increases in parathyroid hormone nor hypotension, per se, were listed within the SPC as adverse events and therefore the information the complainant highlighted was not 'critical' information to the patient selection or dosing of dapagliflozin.

The Panel accepted AstraZeneca's submission that readers would expect the Prescribing and Dosing webpage to include information to support the practicalities of prescribing and to clearly inform readers about dosing in renal impairment.

Whilst the Panel considered that the information on moderate renal impairment drawn out in the 'Special Warnings and precautions for use' section of the Forxiga SPC would have been important information to provide readers, the Panel nonetheless considered the complainant's allegations in the context of the Prescribing and Dosing webpage. Taking into account the content of the SPC and that there were no dose adjustments, no changes in monitoring and no patient selection considerations required in people with moderate renal impairment, the Panel did not consider that the complainant had established that the associated adverse events in relation to increase in parathyroid hormone and hypotension was critical information required on the Prescribing and Dosing webpage of the Forxiga website. The Panel, therefore, based on the narrow allegation in relation to the Prescribing and Dosing webpage, ruled **no breach of Clause 6.1**.

The Panel did not consider that the complainant had made an allegation that the information on the Prescribing and Dosing webpage of the Forxiga website was incapable of substantiation and ruled **no breach of Clause 6.2** in this regard.

Based on its rulings of no breaches of the Code above, the Panel did not consider that it had been established that AstraZeneca had failed to maintain high standards, nor that it had brought discredit upon, or reduced confidence in, the pharmaceutical industry, and ruled **no breach of Clauses 5.1 and 2**, accordingly.

Complaint received **22 June 2023**

Case completed **8 March 2024**