**CASE AUTH/3618/3/22**

# COMPLAINANT v ASTRAZENECA

## Promotion of Forxiga

### CASE SUMMARY

**This case was in relation to dosage claims about Forxiga (dapagliflozin) made by a representative and on a promotional website.**

**The Panel ruled a breach of the following Clause(s) of the 2021 Code in relation to the claims 'Start FORXIGA 10mg today' and 'FORXIGA 10mg. Simple once-daily dosing – start on 10mg, stay on 10mg, no need for uptitration', which had important qualifying safety information about a lower 5mg starting dose for patients with severe hepatic impairment in a small footnote that could have easily been missed:**

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| **Breach of Clause 2** | **Bringing discredit upon, and reducing confidence in, the pharmaceutical industry** |
| **Breach of Clause 5.1** | **Failing to maintain high standards** |
| **Breach of Clause 6.1** | **Providing misleading information** |
| **Breach of Clause 6.2** | **Providing misleading information which was not capable of substantiation** |
| **Breach of Clause 11.2** | **Promotion inconsistent with the summary of product characteristics** |
| **Breach of Clause 14.4** | **Not encouraging the rational use of a medicine** |

**The Panel ruled no breach of the following Clause(s) of the 2021 Code in relation to the allegation that a claim about cardiorenal benefits was incapable of substantiation and for a lack of evidence that a representative misleadingly implied that all patients could start on Forxiga 10mg without referring to the lower 5mg starting dose required for patients with severe hepatic impairment:**

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| **No Breach of Clause 6.2** | **Requirement that information, claims or comparisons must be capable of substantiation** |
| **No Breach of Clause 17.9** | **Requirement that representatives' briefing material must comply with the relevant requirements of the Code** |

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

## FULL CASE REPORT

An anonymous contactable complainant who described him/herself as a health professional complained about the promotion of Forxiga (dapagliflozin), marketed by AstraZeneca.

The complainant referred to a call from an AstraZeneca representative and provided a screenshot from the forxiga.co.uk website (material ref GB-34486). The screenshot provided by the complainant featured claims for Forxiga which included: 'FORXIGA 10 mg. Simple once-daily dosing – start on 10mg, stay on 10mg, no need for uptitration*; For cardiorenal benefits, initiate in patients with eGFR ≥15mL/min/1.73m$^2$ **; Start FORXIGA 10 mg today'.

Beneath the list of claims was an explanation for the single asterisk * which stated: 'In patients with severe hepatic impairment, a starting dose of 5mg is recommended. If well tolerated, the dose may be increased to 10mg.' The explanation for the double asterisk ** was 'Limited experience in initiating Forxiga in patients with eGFR<25/mL/min/1.73m$^2$.'

## COMPLAINT

The complainant stated that he/she had a call from an AstraZeneca sales representative to his/her practice this week. During the discussion the representative informed him/her that 'Forxiga has a simple once daily dosing start on 10mg, stay on 10mg with no need to uptitrate.' The complainant stated that he/she was surprised by this claim as rarely did one encounter treatments like this. Further it made the fact that the medicine had multiple doses seem strange. The complainant was sure the representative was mistaken and so looked at the company website www.forxiga.co.uk (GB-34486). The site had the claim, attached as an image (taken March 2022). The image had 2 claims which the complainant alleged did not reflect the summary of product characteristics (SPC) fully and could easily put patient safety at risk and lead to inappropriate prescribing.

Firstly, the claim about simple dosing start and stay and do not titrate. If patients had severe hepatic impairment a dose of 5mg was recommended and should be titrated; this footnote in small text seemed hidden away and certainly was not raised by the representative. The complainant was sure this could not be a permissible way to represent claims. Surely the industry had high standards. These were medicines and patients with complex health issues. It was unethical to make bold sweeping claims. The complainant alleged this brought the industry into disrepute and explained in part the reputation view his/her colleagues frequently felt regarding pharmaceutical company promotion.

The second issue was the instruction to start Forxiga 10mg today. How could this be possible? For some patients this would not be acceptable. The complainant was deeply concerned by this approach to product claims especially when these were brought in together as 2 points. The complainant was also concerned that the claims also stated for cardio renal benefits initiate in patients with egfr down to 15ml/min/1.73m$^2$ and yet again the footnote claimed to have limited experience in patients with egfr <25. If there was limited experience what statistically proven benefits were shown between 25egfr and 15egfr that substantiated this claim. The complainant trusted that action would be taken to restore the credibility of the industry.

When writing to AstraZeneca, the Authority asked it to consider the requirements of Clauses 6.1, 6.2, 11.2, 14.4, 17.9, 5.1 and 2 of the Code.

**RESPONSE**

AstraZeneca submitted that its response would establish that:

- Dosing information included on the website was in line with the SPC
- Information about 5mg starting dose in patients with severe hepatic impairment was clearly stated on the website
- Sales representatives were fully briefed on all starting doses of Forxiga
- Information on the website supported and provided context for the claim 'Start Forxiga 10mg today'
- Claim for initiation of Forxiga in patients with eGFR > 15mls/min was in line with the SPC

AstraZeneca addressed each of the complainant's allegations according to the relevant clauses of the Code.

1. **Claim: 'Forxiga has a simple once daily dosing - start on 10mg, stay on 10mg with no need to up titrate'.**

   AstraZeneca drew attention to section 4.2 of the SPC which stated that Forxiga could be administered as one single 10mg tablet and could be taken at any time of day with or without food. Furthermore, the recommended starting dose across all three indications (Type 2 diabetes, heart failure and chronic kidney disease) was 10mg dapagliflozin once daily and no dose adjustment or titration was required. Patients also did not require a dose adjustment based upon their renal function and/or age which were often common reasons requiring different or lower starting or maintenance doses of medicines. AstraZeneca acknowledged that this was not the case with all diabetes medications but in the case of Forxiga the information was correct and consistent with the SPC.

2. **Patients with severe hepatic impairment should be started on a 5mg dose.**

   AstraZeneca submitted that in a pharmacokinetic (PK) study (Kasichayanula S *et al* 2011), subjects with mild or moderate hepatic impairment (Child-Pugh classes A and B), mean $C_{max}$ and AUC of dapagliflozin were up to 12% and 36% higher, respectively, compared to healthy matched control subjects. These differences were not considered to be clinically meaningful. In subjects with severe hepatic impairment (Child-Pugh class C) mean $C_{max}$ and AUC of dapagliflozin were 40% and 67% higher than matched healthy controls, respectively. Dapagliflozin was well tolerated by all participants, and no deaths or discontinuations due to adverse events (AE) were reported. In total, 5 AEs occurred (phlebitis, abdominal discomfort, back pain, rash, dizziness); all resolved before study discharge. The degree of hepatic impairment had no apparent effect on the incidence of AEs (Kasichayanula S, *et al* 2011).

   AstraZeneca submitted that in patients with mild or moderate hepatic impairment no dose adjustment was necessary. Given the PK data there was a recommendation to start on the 5mg dose in patients with severe hepatic impairment. This dosing information was clearly provided as part of the promotional material.

   The exact number of patients with type 2 diabetes and severe hepatic impairment in the UK was difficult to quantify but given that approximately 60,000 patients (Williams *et al*

2014) were reported to have cirrhosis of the liver, the absolute numbers of those patients with type 2 diabetes and severe hepatic impairment, defined as Child-Pugh Class 3, was likely to be proportionately low. Therefore, AstraZeneca believed that most patients would start on a dose of 10mg and remained on that dose and therefore the information provided was consistent with SPC and not misleading.

**3. Sales representative did not mention 5mg starting dose for patients with severe hepatic impairment**

AstraZeneca submitted that all representatives had been fully briefed on how to sell Forxiga including the dosing requirements in all populations. They were briefed on the technical aspects of Forxiga using the interactive detail aid (page with dosing information for primary care and for secondary care were provided). A Forxiga SPC test was also used to test sales representative's knowledge, which included a question about dosing in severe hepatic impairment. Sales representatives had to pass this assessment before they could start promoting Forxiga. As it was not possible to identify the health professional who complained it was not possible to investigate if the representative discussed the dosing requirements related to hepatic impairment during the promotional call. Therefore, AstraZeneca did not accept that sufficient evidence had been provided to the contrary.

**4. Claim: 'Start Forxiga at 10mg, today'**

AstraZeneca stated that it did not feel it was inappropriate to ask a health professional to prescribe one of its medicines. This call to action was included on the website alongside all the supporting information regarding the safety, clinical effectiveness and dosing requirements for Forxiga.

**5. Claim: 'Initiate Forxiga in patients eGFR >15mls/min'**

AstraZeneca submitted that Forxiga's cardiovascular and renal benefits were supported by the current marketing authorisation and the clinical trial data references in section 5 of the SPC. Forxiga was indicated for the treatment of adults with insufficiently controlled type 2 diabetes, heart failure with reduced ejection fraction and chronic kidney disease. The SPC referenced a starting dose of 10mg across all three indications and also went onto state that there was no dose adjustment required based upon renal function. Section 4.2 posology and method of administration contained the following statement 'It is not recommended to initiate treatment with dapagliflozin in patients with an estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73m$^2$'.

AstraZeneca therefore submitted that the claim 'initiate Forxiga in patients with eGFR > 15mls/min' was consistent with the SPC and did not require additional qualification. A supporting statement about limited data in those with eGFR < 25ml/min /1.73m$^2$ was, however, also clearly stated on same page. Also, as the glycaemic effect of Forxiga might be lost at lower eGFRs, AstraZeneca submitted that it had provided clear information to the reader that changes to other glycaemic medication might be required in order to maintain $HbA1_c$ control. AstraZeneca submitted that as stated earlier there was no requirement to adjust dose or discontinue Forxiga based upon a patient's renal function.

AstraZeneca denied breaches of Clauses 6.1, 6.2, 11.2, 14.4, 17.9, 5.1 and 2 of the Code.

**Summary**

AstraZeneca submitted that given the information provided above, the claim was consistent with the SPC and provided sufficient information and context for the heath professional to make an informed prescribing decision for their patients, was not misleading and did not put patient safety at risk. AstraZeneca therefore categorically denied all allegations and any suggestions that any of the alleged clauses had been breached.

AstraZeneca stated 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 complainant's allegations appeared to relate to claims about Forxiga on the company's website and a conversation with an AstraZeneca representative; the Panel thus set out its rulings accordingly.

**Forxiga website**

The Panel noted that the webpage containing the claims at issue was titled 'forxiga unlockd (dapagliflozin)' and appeared to form part of the Forxiga promotional website. Below the title appeared three boxes with their respective icons and headings 'chronic kidney disease', 'symptomatic chronic heart failure with reduced ejection fraction' and 'insufficiently controlled type 2 diabetes.' This was followed by a section titled 'New Updated NG28 Guidelines', which included a short overview of the NICE guidelines and a link to access the full guidelines. Beneath this were further Forxiga claims, including the indication and an infographic with the claim 'First and only SGLT-2i approved for the treatment of three diseases.' Towards the bottom of the webpage, before the tools and resources section, were four claims:

- 'FORXIGA 10mg. Simple once-daily dosing – start on 10mg, stay on 10mg, no need for uptitration*
- For cardiorenal benefits, initiate patients with eGFR $\geq$ 15mL/min/1.73m$^2$** If GFR is <45mL/min/1.73m$^2$ and glycaemic efficacy is desired, additional glucose lowering treatment should be considered.
- Overall safety profile of FORXIGA 10mg in CKD and HF patients was consistent with well-established safety profile in T2D
- Start FORXIGA 10mg today'

With regard to the first claim, 'FORXIGA 10mg. Simple once-daily dosing – start on 10mg, stay on 10mg, no need for uptitration*', and accompanying footnote, the Panel noted the complainant's allegations that this claim: did not fully reflect the SPC, could lead to inappropriate prescribing, the footnote about severe hepatic impairment was in small text, it was a bold sweeping claim, could put patient safety at risk and brought the industry into disrepute.

The Panel noted that the claim was in blue bold font, in a similar size to the subheadings, and the corresponding footnote was in much smaller non-bold black font beneath the list of the four claims. The footnote stated 'In patients with severe hepatic impairment, a starting dose of 5mg is recommended. If well tolerated, the dose may be increased to 10mg'.

The Panel noted AstraZeneca's submission that according to Section 4.2 of the summary of product characteristics (SPC), Forxiga could be administered as one single 10mg tablet and could be taken at any time of day with or without food; the recommended starting dose across all three indications (Type 2 diabetes, heart failure and chronic kidney disease) was 10mg dapagliflozin once daily and no dose adjustment or titration was required. AstraZeneca submitted that patients did not require a dose adjustment based upon their renal function and/or age.

The Panel noted, however, that Section 4.2 of the SPC, under Special Populations, Hepatic Impairment, stated 'No dose adjustment is necessary for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg'. Further, Section 4.4 Special warnings and precautions for use, under Hepatic impairment, stated that 'there is limited experience in clinical studies in patients with hepatic impairment. Dapagliflozin exposure is increased in patients with severe hepatic impairment.'

The Panel noted AstraZeneca's submission that given the data from a pharmacokinetic study (Kasichayanula *et al* 2011), there was a recommendation to start on the 5mg dose in patients with severe hepatic impairment.

It appeared to the Panel that the only mention of starting on 5mg Forxiga in patients with severe hepatic impairment on the webpage at issue was within the footnote corresponding to the first claim.

The supplementary information to Clause 6.1 stated that, in general, claims should not be qualified by the use of footnotes and the like. The Panel considered the content and layout of the webpage, including the information between the claim at issue and the corresponding footnote, and the difference in font size, colour and boldness of the two.

In the Panel's view, a busy health professional might read the claim 'FORXIGA 10mg. Simple once-daily dosing – start on 10mg, stay on 10mg, no need for uptitration' without scrolling further down the webpage to see the qualifying small footnote about severe hepatic impairment and therefore might incorrectly assume that Forxiga could be started on 10mg without uptitration in all patients, which was not so.

The Panel did not accept AstraZeneca's submission that as the numbers of patients with type 2 diabetes and severe hepatic impairment were likely to be proportionately low, most patients would start on a dose of 10mg and remain on that dose and thus the information was consistent with the SPC and not misleading. In the Panel's view, regardless of how many people might need to start on 5mg, it was fundamental that AstraZeneca did not misleadingly imply that all patients could start on 10mg.

The Panel considered the immediate and overall impression of the webpage. The Panel considered that promoting the initiation of Forxiga 10mg with no uptitration, without clearly bringing to the reader's attention that patients with severe hepatic impairment were recommended to start on Forxiga 5mg prior to uptitration if well tolerated, meant that the claim 'FORXIGA 10mg. Simple once-daily dosing – start on 10mg, stay on 10mg, no need for uptitration*' was misleading. Read in isolation, the claim implied that all patients could start on 10mg which was not so. The Panel did not consider that the claim could stand alone without the footnote and thus ruled **a breach of Clause 6.1**.

Noting the SPC stated 'In patients with severe hepatic impairment, a starting dose of 5 mg is recommended', the Panel considered that the misleading impression given by the claim when read without its footnote was incapable of substantiation and inconsistent with the SPC. The Panel ruled **a breach of Clauses 6.2** and **11.2** accordingly.

In the Panel's view, the misleading impression given was such that readers would assume that they could start all patients on Forxiga 10mg which was not so. The Panel considered that the claim did not encourage the rational use of the medicine and ruled **a breach of Clause 14.4**.

The Panel further noted the complainant's allegation that the fourth claim 'Start FORXIGA 10mg today' would not be an acceptable starting dose for some patients.

The Panel noted AstraZeneca's submission that this call to action was included on the website alongside all the supporting information regarding the safety, clinical effectiveness and dosing requirements for Forxiga. The Panel did not have the safety, clinical effectiveness and dosing pages before it. Nonetheless, a health professional may only look at the home page of a website and therefore the claims on the homepage should standalone and not require a health professional to search the website for supporting information.

The Panel noted the content of section 4.2 of the Forxiga SPC as referred to above.

The Panel considered that it was important to provide accurate information about dosing, bearing in mind potential patient safety implications. In the Panel's view, the claim 'Start Forxiga 10mg today' misleadingly implied that a dose of 10mg could be started today in all patients. Whilst a footnote in relation to dosing in severe hepatic impairment appeared beneath this claim, the Panel noted that the asterisk was associated with a different claim (as ruled on above) for which the footnote was in much smaller, non-bold font of a different colour.

The Panel, noting that claims must standalone, considered that a busy health professional might not read the small footnote and therefore be left with the misleading impression that all patients could start on Forxiga 10 mg today which was not so. Given the recommendation in the SPC regarding a starting dose of 5mg in patients with severe hepatic impairment, the Panel considered that the claim 'Start FORXIGA 10mg today' was misleading, and that the misleading impression given was inconsistent with the SPC and incapable of substantiation. The Panel therefore ruled **breaches of Clauses 6.1, 6.2 and 11.2**. The Panel further considered that the claim did not encourage the rational use of Forxiga and thus ruled **a breach of Clause 14.4** in this regard.

Noting its rulings of breaches of the Code above in relation to both claims, the Panel considered that AstraZeneca had failed to maintain high standards. **A breach of Clause 5.1** was ruled.

The Panel considered that patient safety was of the utmost importance. Examples of activities likely to lead to a breach of Clause 2 included prejudicing patient safety. The Panel considered that the claims 'Start FORXIGA 10mg today' and 'FORXIGA 10mg. Simple once-daily dosing – start on 10mg, stay on 10mg, no need for uptitration*', the latter of which had an associated footnote with qualifying and important safety information that could easily be missed by a busy health professional, was such that AstraZeneca had brought discredit upon and reduced confidence in the pharmaceutical industry, and **a breach of Clause 2** was ruled.

With regard to the second of the four claims, the Panel noted the complainant's allegation that it could not be substantiated based on the footnote that there was limited experience in initiating Forxiga in patients with eGFR < 25mL/min/1.73m$^2$. The Panel noted the full claim stated: 'For cardiorenal benefits, initiate in patients with eGFR ≥ 15mL/min/1.73m$^2$** If GFR is <45mL/min/1.73m$^2$ and glycaemic efficacy is desired, additional glucose lowering treatment should be considered'. The explanation for the double asterisk, which stated '** Limited experience in initiating FORXIGA in patients with eGFR <25/mL/min/1.73m$^2$', was provided in much smaller, non-bold font of a different colour beneath the four claims.

The Panel noted AstraZeneca's submission that Forxiga's cardiovascular and renal benefits were supported by the current marketing authorisation and the clinical trial data references in Section 5 of the SPC. The Panel noted AstraZeneca's submission that there was no dose adjustment required based upon renal function.

The Panel noted that Section 4.2 Posology and method of administration, Renal impairment, stated that 'it is not recommended to initiate treatment with dapagliflozin in patients with an estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73m$^2$.

In patients with type 2 diabetes mellitus, the glucose lowering efficacy of dapagliflozin is reduced when eGFR is < 45 mL/min/1.73m$^2$ and is likely absent in patients with severe renal impairment. Therefore, if eGFR falls below 45 mL/min/1.73m$^2$, additional glucose lowering treatment should be considered in patients with type 2 diabetes mellitus.' Section 4.4 Special warnings and precautions for use, Renal impairment, of the SPC stated 'There is limited experience with initiating treatment with dapagliflozin in patients with eGFR < 25 mL/min/1.73m$^2$, and no experience with initiating treatment in patients with eGFR < 15 mL/min/1.73m$^2$. Therefore, it is not recommended to initiate treatment with dapagliflozin in patients with eGFR < 15 mL/min/1.73m$^2$'.

In the Panel's view, whilst the footnote 'Limited experience in initiating FORXIGA in patients with eGFR <25/mL/min/1.73m$^2$' was not required to qualify the claim 'For cardiorenal benefits, initiate in patients with eGFR ≥ 15mL/min/1.73m$^2$', it was useful information that could have been presented alongside the claim rather than as a footnote. Nonetheless, the Panel noted the complainant's narrow allegation that the claim was incapable of substantiation and considered that the complainant had not established that the claim 'For cardiorenal benefits, initiate in patients with eGFR ≥ 15mL/min/1.73m$^2$' was not capable of substantiation and **no breach of Clause 6.2** of the Code was ruled in this regard.

**Sales representative**

The Panel noted the complainant's allegation that the sales representative who made the claim 'Forxiga has a simple once daily dosing start on 10mg, stay on 10mg with no need to uptitrate' did not refer to the need for patients with severe hepatic impairment to start at a dose of 5mg.

The complainant was anonymous to AstraZeneca and therefore the company submitted that it was unable to investigate if the representative discussed the dosing requirements related to severe hepatic impairment during the promotional call in question. The Panel considered that a judgement had to be made on the available evidence bearing in mind the extreme dissatisfaction usually necessary on the part of an individual before he or she was moved to submit a complaint.

The Panel noted AstraZeneca's submission that all representatives had been fully briefed on how to sell Forxiga including the dosing requirements in all populations and were briefed on the technical aspects of Forxiga using the interactive detail aid. The Panel noted that the dosing pages from the interactive detail aids for primary and secondary care had a claim at the top stating 'FORXIGA 10mg offers simple dosing[1].' Beneath this in a larger font there was a claim stating, 'START ON 10 MG STAY ON 10 MG*'. The asterisk led to a footnote in a much smaller, non bold font of a different colour, at the bottom of the page, which stated 'In patients with severe hepatic impairment, a starting dose of 5mg is recommended. If well tolerated, the dose may be increased to 10 mg.'

Clause 17.9 of the Code stated that representatives' briefing material must comply with the relevant requirements of the Code and must not advocate, either directly or indirectly, any course of action which would be likely to lead to a breach of the Code. Companies must prepare detailed briefing material for representatives on the technical aspects of each medicine which they will promote.

The Panel noted AstraZeneca's submission that a Forxiga SPC test was also used to test sales representatives' knowledge, which included a question about dosing in severe hepatic impairment and representatives had to pass this assessment before they could start promoting Forxiga. In the Panel's view, an SPC test in itself was insufficient as briefing material in relation to the claims being used in promotional material.

Whilst the Panel noted that AstraZeneca had not submitted any briefing material which instructed representatives to communicate that the starting dose was 5mg in patients with severe hepatic impairment whenever the claim 'start on 10 mg stay on 10 mg' was used, the Panel had no evidence before it that such information was not communicated by the representative during the call in question as alleged. Based on the limited evidence provided by either party and the narrow allegation, the Panel ruled **no breach of Clause 17.9.**

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**Complaint received** **11 March 2022**

**Case completed** **3 April 2023**