CASE AUTH/3506/4/21

COMPLAINANT v DAIICHI-SANKYO

Journal advertisement for Lixiana (edoxaban)

A complainant, who was originally contactable but later became non-contactable, complained about a two-page journal advertisement by Daiichi-Sankyo UK Ltd for Lixiana (edoxaban) which appeared in Guidelines in Practice (March 2021, Volume 24, Issue 3).

The advertisement included an image of a patient with multiple heads alongside the claim '24 HOUR STROKE PREVENTION IN ONE DOAC PILL'. Below this, the indication for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) and one or more risk factors such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemia attack was given, followed by the statement 'In patients with NVAF and high creatinine clearance, there is a trend towards decreasing efficacy with increasing creatinine clearance for edoxaban vs. well-managed warfarin, therefore careful evaluation of thromboembolic and bleeding risk is necessary before initiation'. The bottom of the advertisement included both 30mg and 60mg Lixiana pack shots below which was the claim 'ONCE-DAILY DOAC FOR YOUR AGEING PATIENTS WITH NVAF'. The bottom of the page stated 'For more information please visit www.lixiana.co.uk'. The prescribing information appeared overleaf.

In response to a question from the case preparation manager, the complainant clarified in a further complaint (Case AUTH/3507/5/21) that in relation to this present case (Case AUTH/3506/4/21), the journal advertisement he/she was referring to was a hard copy print journal.

Allegation 1 – use of illustration

The complainant referred to the image within the advertisement which contained a lot of heads with the claim '24 hour stroke prevention in one DOAC [Direct Oral AntiCoagulant] pill' written in pink in prominence next to the patient heads image. The licence for the product was only for those equal to, or over, 75 years old. Some pictures of the people in the numerous heads image were less than 75 years old. The complainant alleged that this made the advertisement misleading and not in line with the licence especially as if a busy health professional was looking at this advertisement at a quick glance, they could easily assume the medicine could be used in patients aged lower than 75 as this was not written in prominence next to the picture.

Allegation 2 – dosing

The complainant stated that further down the advertisement, there was pack images of 60mg Lixiana and 30mg Lixiana, with a claim stating 'ONCE-DAILY DOAC FOR YOUR AGEING PATIENTS WITH NVAF [nonvalvular atrial fibrillation]' directly underneath the

two pack size pictures. This complainant alleged that this was misleading as a busy health professional or even those looking at the advertisement in detail could wrongly interpret that either the 60mg or 30mg dosage could be used in any ageing patient with NVAF. The summary of product characteristics (SPC) for Lixiana clearly specified that there were certain groups of patients who MUST be given 30mg (low body weight, renal impairment and use of certain p-gb inhibitors). This claim and the pack sizes together were allegedly misleading and caused potential patient harm without clear segregation. Equally, it was important for a health professional to understand which patients were eligible for 60mg vs 30mg so high risk patients were not under anticoagulated which would lead to a risk of stroke.

Allegation 3 – reference to prescribing information

The complainant noted that the prescribing information was overleaf and the Code was clear in that if the prescribing information was overleaf, at either the beginning or the end of the advertisement, a reference to where it could be found must appear on the outer page of the other page of the advertisement in a type size such that a lower case 'x' was no less than 2mm in height. This was not provided on the advertisement. Such a basic error was surprising considering previous issues around promotion of Lixiana and also subsequent audits Daiichi-Sankyo were going through. There was a clear lack of learning.

The detailed response from Daiichi-Sankyo is given below.

Allegation 1

The Panel noted that the advertisement appeared to be for both Lixiana 30mg and 60mg which according to their SPCs were both indicated, *inter alia*, for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).

The Panel noted Daiichi-Sankyo's submission that the complainant was incorrect when stating that Lixiana was only licensed in those aged 75 years or over; the wording of the licensed indication was such that the list of risk factors was not exhaustive and only one risk factor was required which did not necessarily have to be age ≥75 years.

The Panel did not consider that the complainant had established that Lixiana had been promoted in a manner that was inconsistent with its licensed indication or that the image was misleading as alleged and no breaches of the Code were ruled including no breach of Clause 2.

Allegation 2

The Panel noted Daiichi-Sankyo's submission that for NVAF, the recommended dose was 60mg edoxaban once-daily, but the recommended dose of 30mg edoxaban once-daily was for patients with one or more of the following clinical factors which was stated in the prescribing information: Moderate or severe renal impairment (creatinine clearance (CrCl) 15 - 50 mL/min); Low body weight ≤ 60 kg; and Concomitant use of the following P-glycoprotein (P-gp) inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole.

The Panel noted Daiichi-Sankyo's submission that it was clear from the advertisement that there were two strengths available. In the Panel's view, health professionals would therefore refer to the prescribing information and/or SPC to determine which dose was appropriate for each patient. The Panel noted that the complainant bore the burden of proof and did not consider that he/she had established that the claim in combination with the 30mg and 60mg pack shot implied that either the 60mg or 30mg dosage could be used in any ageing patient with NVAF as alleged. No breaches of the Code were ruled including no breach of Clause 2.

Allegation 3

The Panel noted Daiichi-Sankyo's submission that such reference to where the prescribing information appeared was missing from the advertisement which was an oversight and a breach of the Code was thus ruled as acknowledged by Daiichi-Sankyo.

The Panel noted that the bottom of the full-page advertisement stated, in large prominent typeface, 'For more information please visit www.lixiana.co.uk'. In the Panel's view, this statement might have led readers to assume there was no further information about Lixiana within the journal advertisement, which was not so; the prescribing information was overleaf.

The Panel noted Daiichi-Sankyo's submission that the Lixiana marketing team were no longer running advertisements with prescribing information overleaf. Nonetheless, the Panel considered that failure to include reference to where prescribing information could be found, and the impression that there was no further information about Lixiana within the journal advertisement, given that readers were told to visit www.lixiana.co.uk for more information, meant that Daiichi-Sankyo had failed to maintain high standards and a breach of the Code was ruled.

A complainant, who was originally contactable but later became non-contactable, complained about a journal advertisement by Daiichi-Sankyo UK Ltd for Lixiana (edoxaban) with the job code EDX/20/1152 and with the date of preparation November 2020 which appeared in the MGP Guidelines in Practice journal (March 2021, Volume 24, Issue 3). The advertisement was on page 11 of the journal with the prescribing information overleaf on page 12.

The advertisement in question included an image of a patient with multiple heads alongside the claim '24 HOUR STROKE PREVENTION IN ONE DOAC PILL'. Below this, the indication for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) and one or more risk factors such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemia attack was given, followed by the statement 'In patients with NVAF and high creatinine clearance, there is a trend towards decreasing efficacy with increasing creatinine clearance for edoxaban vs. well-managed warfarin, therefore careful evaluation of thromboembolic and bleeding risk is necessary before initiation'. The bottom of the advertisement included both 30mg and 60mg Lixiana pack shots below which was the claim 'ONCE-DAILY DOAC FOR YOUR AGEING PATIENTS WITH NVAF'. The bottom of the page stated 'For more information please visit www.lixiana.co.uk'. The prescribing information appeared overleaf.

In response to a question from the case preparation manager, the complainant clarified in a further complaint (Case AUTH/3507/5/21) that in relation to this present case (Case

AUTH/3506/4/21), the journal advertisement he/she was referring to was a hard copy print journal.

COMPLAINT

Allegation 1 – use of illustration

The complainant submitted that the image within the advertisement contained a lot of heads with the claim '24 hour stroke prevention in one DOAC [Direct Oral AntiCoagulant] pill' written in pink in prominence next to the patient heads image. The licence for the product was only for those equal to, or over, 75 years old. Some pictures of the people in the numerous heads image were less than 75 years old. The complainant alleged that this made the advertisement misleading and not in line with the licence especially as if a busy health professional was looking at this advertisement at a quick glance, they could easily assume the medicine could be used in patients aged lower than 75 as this was not written in prominence next to the picture. This was allegedly in breach of Clauses 3.2, 7.2, 9.1 and 2 of the Code.

Allegation 2 - dosing

The complainant submitted that further down the advertisement, there was pack images of 60mg Lixiana and 30mg Lixiana, with a claim stating 'ONCE-DAILY DOAC FOR YOUR AGEING PATIENTS WITH NVAF [nonvalvular atrial fibrillation]' directly underneath the two pack size pictures. This complainant alleged that this was misleading as a busy health professional or even those looking at the advertisement in detail could wrongly interpret that either the 60mg or 30mg dosage could be used in any ageing patient with NVAF. The summary of product characteristics (SPC) for Lixiana clearly specified that there were certain groups of patients who MUST be given 30mg (low body weight, renal impairment and use of certain p-gb inhibitors). This claim and the pack sizes together were allegedly misleading and caused potential patient harm without clear segregation. Equally, it was important for a health professional to understand which patients were eligible for 60mg vs 30mg so high risk patients were not under anticoagulated which would lead to a risk of stroke. This was allegedly in breach of Clauses 3.2, 7.2, 7.4, 9.1 and 2.

Allegation 3 – reference to prescribing information

The complainant submitted that the prescribing information was overleaf and Clause 4.7 of the Code was clear in that if the prescribing information was overleaf, at either the beginning or the end of the advertisement, a reference to where it could be found must appear on the outer page of the other page of the advertisement in a type size such that a lower case 'x' was no less than 2mm in height. This was not provided on the advertisement. Such a basic error was surprising considering previous issues around promotion of Lixiana and also subsequent audits Daiichi-Sankyo were going through. There was a clear lack of learning. The complainant alleged that this particular aspect breached Clauses 4.7 and 9.1.

When writing to Daiichi-Sankyo, the Authority asked it to consider the requirements of Clauses 3.2, 4.7, 7.2, 7.4, 9.1 and 2 of the Code as cited by the complainant.

RESPONSE

Daiichi-Sankyo submitted that it took its obligations under the Code seriously, strove to maintain high standards and behaved responsibly and ethically at all times.

Daiichi-Sankyo submitted that the allegations above were related to an advertisement placed in a MGP Guidelines in Practice journal (Job Code EDX/20/1152 | Date of preparation: November 2020).

Allegation 1

Daiichi-Sankyo denied breaches of Clauses 3.2, 7.2, 9.1 and 2.

Daiichi-Sankyo submitted that the complainant was incorrect that 'The licence for the product was only for those equal to or over 75 years old'.

The section directly underneath the imagery stated the licensed indication: 'Lixiana is indicated for: prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA)'. The wording 'such as' in the licence indicated that this was not an exhaustive list of risk factors for which edoxaban was indicated, so a patient might have risk factors that were not specifically mentioned that would still make them eligible for edoxaban. Only one risk factor was required, and this did not necessarily have to be age ≥75 years.

Daiichi-Sankyo submitted that in this case, the promotion of edoxaban was in line with the terms of its marketing authorisation and was therefore consistent with the particulars listed in its summary of product characteristics (SPC), and therefore Daiichi-Sankyo was not in breach of Clause 3.2.

Daiichi-Sankyo submitted that the complainant stated that 'Some of pictures of the people in the numerous heads were less than 75 years old. This made the advert misleading and not in line with the licence especially as if a busy healthcare professional was looking at this advert at a quick glance, they could easily assume the drug could be used in patients aged lower than 75 as this was not written in prominence next to the picture'.

Lixiana was indicated for: prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as:

- congestive heart failure
- hypertension
- age ≥75 years
- diabetes mellitus
- prior stroke or transient ischaemic attack (TIA).

As such, age of ≥75 years was just one of the risk factors required for its indication, as stated above. Therefore, the imagery in the advertisement was not a misleading picture as the licence did include patients less than 75 years of age. Therefore, Daiichi-Sankyo denied any breach of Clause 7.2. In addition, Daiichi-Sankyo submitted that there was no evidence that high standards had not been maintained (no breach of Clause 9.1) or that confidence in the industry had been reduced (no breach of Clause 2).

Allegation 2

Daiichi-Sankyo noted that the complainant stated that 'Further down the advert, there was pack images of 60mg Lixiana and 30mg Lixiana, with a claim stating ONCE-DAILY DOAC FOR YOUR AGEING PATIENTS WITH NVAF directly underneath the 2 pack size pictures. The complainant alleged that this was misleading as a busy healthcare professional or even those looking at the advert in detail could wrongly interpret that either the 60mg or 30mg dosage could be used in any ageing patient with NVAF'.

Daiichi-Sankyo submitted that there were pack shots of both available doses of edoxaban (60mg and 30mg), as it was important for prescribers to be aware that both doses were once-daily treatments for stroke prevention in patients with NVAF, according to the claim which was consistent with the indications in the marketing authorisation and SPC.

For NVAF the recommended dose was 60mg edoxaban once-daily, but the recommended dose of 30mg edoxaban once-daily was for patients with one or more of the following clinical factors:

- Moderate or severe renal impairment (creatinine clearance (CrCl) 15 - 50 mL/min).
- Low body weight ≤ 60 kg.
- Concomitant use of the following P-glycoprotein (P-gp) inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole.

Daiichi-Sankyo submitted that the above criteria for recommendation of dose reduction was clearly stated in the prescribing information and the prescribing information stated that the SPC should be consulted prior to prescribing.

Therefore, Daiichi-Sankyo did not believe the advertisement was misleading because both pack sizes were within the marketing authorisation, and the dose reduction criteria was clear within both the SPC and prescribing information (no breach of Clause 7.2) and it was in line with its marketing authorisation and licensed indications (no breach of Clause 3.2).

Daiichi-Sankyo submitted that the complainant stated that 'The SPC for Lixiana clearly specified that there were certain groups of patients who MUST be given 30mg (low body weight, renal impairment and use of certain p-gb inhibitors)'.

The complainant was incorrect in his/her quotation of the SPC. The wording in the SPC under 'Posology' stated:

> 'For NVAF (and VTE) the recommended dose is 30 mg edoxaban once daily in patients with one or more of the following clinical factors:
>
> - Moderate or severe renal impairment (creatinine clearance (CrCl) 15 - 50 mL/min)
> - Low body weight ≤ 60 kg
> - Concomitant use of the following P-glycoprotein (P-gp) inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole.'

Daiichi-Sankyo submitted that the complainant stated 'This claim and the pack sizes together were misleading and caused potential patient harm without clear segregation'.

The advertisement showed that both pack sizes were available within the UK in order to inform health professionals about the available licensed doses of edoxaban which were appropriate to both the 30mg once-daily and the 60mg once-daily; the dose reduction criteria were stated in both the SPC and the prescribing information. Daiichi-Sankyo submitted that there was no Code requirement for the specific criteria for the prescribing of each dose to be contained within the body of the advertisement itself. The licensed indication and dose reduction criteria were clearly specified within the prescribing information and fully within the SPC.

The complainant stated: 'Equally it was important for an HCP to understand which patients were eligible for 60mg vs 30mg so high risk patients were not under anticoagulated which would lead to a risk of stroke'.

Daiichi- Sankyo submitted that the dose requirements (including the recommendations for dose reduction) for the prevention of stroke and systemic embolism in patients with NVAF were clear in both the SPC and prescribing information as stated above. The recommended dose of edoxaban in these indications was 60mg once-daily, with the option of a 30mg once-daily dose for those patients who met certain criteria, as detailed above. Therefore, Daiichi-Sankyo denied any breach of Code clauses.

Daiichi-Sankyo submitted that its advertisement was in line with the marketing authorisation and licensed indication for edoxaban, and therefore it denied any breach of Clause 3.2.

The claims within the advertisement and the doses shown on the pack shots were in line with the marketing authorisation and the indication for edoxaban. Therefore, this was not misleading, and Daiichi-Sankyo denied a breach of Clause 7.2. As such, there was no breach of Clause 7.4 as the claims were substantiated by the SPC in line with the marketing authorisation and licensed indication for edoxaban.

In addition, there was no evidence that high standards had not been maintained (no breach of Clause 9.1) or that the advertisement and the information about the pack shots had prejudiced patient safety. Daiichi-Sankyo UK submitted it took patient safety very seriously: the information and claims within the advertisement was in line with the SPC recommendations for edoxaban. Therefore, Daiichi-Sankyo UK denied a breach of Clause 2.

Allegation 3

Daiichi-Sankyo acknowledged that a declaration clearly stating that the prescribing information would be found overleaf was missing from the advertisement; this was an oversight on its part, and the Lixiana Marketing Team were no longer running advertisements with prescribing information overleaf. Daiichi-Sankyo therefore agreed that Clause 4.7 had been breached. Daiichi-Sankyo UK denied that high standards had not been maintained and therefore no breach of Clause 9.1.

Conclusion

Daiichi-Sankyo strongly denied all breach allegations, apart from Clause 4.7. Daiichi-Sankyo submitted that it trusted that the PMCPA would agree that it had taken this matter seriously,

maintained high standards, and had not, in any way, prejudiced patient safety in publishing the journal advertisement at issue.

PANEL RULING

Allegation 1

The Panel noted that the advertisement contained an image which appeared to portray multiple heads of patients. The Panel noted the complainant's concern that some of the people within the image were less than 75 years old which implied to a busy health professional viewing the advertisement that the medicine could be used in patients aged lower than 75, which was not in line with the product's licensed indication.

The Panel noted that the advertisement appeared to be for both Lixiana 30mg and 60mg which according to their SPCs were both indicated, inter alia, for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).

The Panel noted Daiichi-Sankyo's submission that the complainant was incorrect when stating that Lixiana was only licensed in those aged 75 years or over; the wording of the licensed indication was such that the list of risk factors was not exhaustive and only one risk factor was required which did not necessarily have to be age ≥75 years.

The Panel did not consider that the complainant had established that Lixiana had been promoted in a manner that was inconsistent with its licensed indication or that the image was misleading as alleged and no breach of Clauses 3.2 and 7.2 were ruled. The Panel consequently ruled no breach of Clauses 9.1 and 2.

Allegation 2

The Panel noted the complainant's allegation that the inclusion of both the 30mg and 60mg pack shots, directly above the claim 'ONCE-DAILY DOAC FOR YOUR AGEING PATIENTS WITH NVAF', misleadingly implied that either the 60mg or 30mg dosage could be used in any ageing patient with NVAF, which was not so.

The Panel noted Daiichi-Sankyo's submission that for NVAF, the recommended dose was 60mg edoxaban once-daily, but the recommended dose of 30mg edoxaban once-daily was for patients with one or more of the following clinical factors which was stated in the prescribing information: Moderate or severe renal impairment (creatinine clearance (CrCl) 15 - 50 mL/min); Low body weight ≤ 60 kg; and Concomitant use of the following P-glycoprotein (P-gp) inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole.

The Panel noted Daiichi-Sankyo's submission that it was clear from the advertisement that there were two strengths available. In the Panel's view, health professionals would therefore refer to the prescribing information and/or SPC to determine which dose was appropriate for each patient. The Panel noted that the complainant bore the burden of proof and did not consider that he/she had established that the claim in combination with the 30mg and 60mg pack shot implied that either the 60mg or 30mg dosage could be used in any ageing patient with NVAF as alleged. No breach of Clauses 3.2, 7.2, 7.4, 9.1 and 2 was ruled.

Allegation 3

The Panel noted that Clause 4.7 of the 2019 Code stated that in the case of a printed journal advertisement, where the prescribing information appears overleaf at either the beginning or the end of the advertisement, a reference to where it could be found must appear on the outer page of the other page of the advertisement in a type size such that a lower case 'x' is no less than 2mm in height.

The Panel noted Daiichi-Sankyo's submission that such reference was missing from the advertisement which was an oversight and a breach of Clause 4.7 was thus ruled as acknowledged by Daiichi-Sankyo.

The Panel noted that the bottom of the full-page advertisement stated, in large prominent typeface, 'For more information please visit www.lixiana.co.uk'. In the Panel's view, this statement might have led readers to assume there was no further information about Lixiana within the journal advertisement, which was not so; the prescribing information was overleaf.

The Panel noted Daiichi-Sankyo's submission that the Lixiana marketing team were no longer running advertisements with prescribing information overleaf. Nonetheless, the Panel considered that failure to include reference to where prescribing information could be found, and the impression that there was no further information about Lixiana within the journal advertisement, given that readers were told to visit www.lixiana.co.uk for more information, meant that Daiichi-Sankyo had failed to maintain high standards and a breach of Clause 9.1 was ruled.

Complaint received **23 April 2021**

Case completed **6 December 2021**