CASE AUTH/3497/3/21

COMPLAINANT v DAIICHI SANKYO

Lixiana (edoxaban) websites

An anonymous complainant, who was originally contactable but later became non-contactable complained about two Daiichi-Sankyo websites for Lixiana (edoxaban).

The complainant alleged that two standalone websites, for a product that could be dangerous to patients if used incorrectly, had multiple failings and errors which did not follow the principles of patient safety.

The detailed response from Daiichi Sankyo is given below.

A Lixiana website (https://lixiana-hcp.co.uk/) ref EDX/21/0176, Date of preparation March 2021 and ref EDX/20/1123, Date of preparation December 2020))

1 Claims 'Your choice for ageing patients with NVAF' and 'Real-world evidence reinforces Lixiana as your DOAC [direct oral anticoagulant] of choice for ageing patients with NVAF[1,2]'

The complainant alleged that the headline claim, 'your choice for ageing patients with NVAF [non-valvular atrial fibrillation]' at the start of the page was misleading and could not be substantiated as Lixiana was only licensed for an age group of ≥75 years in patients with NVAF. It was not appropriate to use such a broad claim in reference to ageing as this could be subjective to interpretation, for example, a 60 year old with NVAF could be seen as ageing but was not suitable for Lixiana treatment.

The complainant alleged that another page with the headline claim 'Real-world evidence reinforces Lixiana as your DOAC of choice for ageing patients with NVAF[1,2]' did not mention the age groups in reference to what the licence was. Health professionals could access any page in isolation, so all pages needed to standalone.

The Panel noted that 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)'. The Panel noted Daiichi-Sankyo's submission that as patients with NVAF aged, they developed more comorbidities and risk factors which put them at increased risk of stroke and systemic embolism.

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 use of the wording 'such as' indicated that the list of risk factors was not exhaustive and only one risk factor was required to be eligible for Lixiana, which did not necessarily have to be

age ≥75 years. The Panel did not consider that the complainant had established that the claims in question were misleading or incapable of substantiation as alleged and, based on the complainant's narrow allegation, no breaches of the Code were ruled in relation to each claim including no breach of Clause 2.

2 Claim 'Efficacy and safety profile even when used with appropriate dose reduction'

The complainant alleged that referring to safety profile within a dose reduction claim implied that Lixiana was safe and did not have side effects even when dosage was reduced. Lixiana could be fatal with some side effects and the complainant alleged that to downgrade the safety implications with such a claim put patient safety at risk in breach of the Code.

The Panel noted Daiichi-Sankyo's submission that the claim was intended to convey that the efficacy and safety profile for edoxaban had been investigated at the standard dose as well as with an appropriately reduced dose and that no claim was made as to what that efficacy and safety profile was. The Panel considered that there was a difference between a medicine being described as 'safe' and referring to the 'safety profile' of a medicine. In the Panel's view, it was not unacceptable to refer to a medicine's safety profile which would likely be interpreted as there being safety information available about the medicine. The Panel considered that, although the claim was somewhat ambiguous, the complainant had not established that it implied that Lixiana was safe and lacked side effects as alleged. The Panel consequently ruled no breaches of the Code including no breach of Clause 2.

3 Claim 'Lactose not listed as an excipient'

The complainant alleged that the claim 'Lactose not listed as an excipient' put patient safety at risk as Daiichi-Sankyo could not guarantee that there had been no contact with lactose during manufacture. This would be a major risk for patients with lactose intolerance as they could have anaphylaxis to lactose. Ironically, this extra information about lactose being in potential contact during manufacture was at the bottom of the page, presented as a footnote. The claim that lactose was not an excipient should have had this important wording around contact during manufacture directly below or adjacent to the claim about lactose as an excipient as opposed to hidden as a footnote.

The Panel noted that the claim 'Lactose not listed as an excipient[iii]' appeared in bold typeface under the section 'Lixiana – simple and convenient once-daily dosing in NVAF[5]', alongside an icon of what appeared to be a milk carton which had '0%' on it. The Panel noted that the reader was directed to a footnote 'We cannot guarantee that there has been no contact with lactose during manufacture. Use with caution in patients that have had severe anaphylaxis with lactose products'. The caution was referenced to a poster by De Groot JR et al presented at ESC 2019.

The Panel considered the immediate and overall impression and in the Panel's view the claim was misleading. Whilst the Panel noted that lactose was not listed as an excipient in the Lixiana SPC, when the claim was read in isolation without the footnote, the proactive provision of the statement 'lactose not listed as an excipient', alongside the icon of a milk carton which had 0% on it, implied that there would be no concerns using Lixiana in patients with a lactose allergy which was not so; according to the footnote,

there was no guarantee that there had been no contact with lactose during manufacture and there was a caveat to use Lixiana with caution in patients that have had severe anaphylaxis with lactose products. The Panel considered that a busy health professional might not have read the important information in the footnote which should have appeared immediately alongside, and with equal prominence to, the claim in question. The Panel therefore ruled breaches of the Code including that Daiichi-Sankyo had failed to maintain high standards.

Clause 2 was a sign of particular censure and was reserved for such use. The Panel noted Daiichi-Sankyo's submission that lactose was not listed as an excipient in the Lixiana SPC and was not expected to be present in Lixiana but it had included the footnote out of an abundance of caution. The Panel noted its rulings of breaches of the Code above and considered that, on balance, these adequately covered the matter; in the Panel's view, a breach of Clause 2 was not warranted in the particular circumstances of this case and, on balance, no breach of Clause 2 was ruled.

4 Claim relating to using 30mg of edoxaban in certain circumstances which mentioned low renal function of creatinine clearance between 15-50ml/min

The complainant noted that the claim related to using 30mg of edoxaban in certain circumstances which mentioned low renal function of creatinine clearance between 15-50ml/min. However, in patients with end stage renal disease or on dialysis, Lixiana was not recommended (the complainant referred to Sections 4.2 and 5.2 of the SPC). That information should have been provided as a busy health professional reading the page or someone not experienced with Lixiana usage could interpret the claim in a misleading fashion. Information should always be fair and balanced and should not have been omitted by only mentioning a certain renal function which suited Daiichi-Sankyo.

The Panel noted that under the heading 'Lixiana – simple and convenient once-daily dosing in NVAF' beneath a subheading in bold font '30mg Reduced dose', it referred to a dose of 30mg once daily in patients with one or more factors that increased the risk of bleeding including, *inter alia*, renal impairment, which appeared in bold font next to an image of the kidneys. CrCl 15-50ml/min appeared below in less prominent font. The Panel noted that CrCl 15-50ml/min was described as moderate or severe renal impairment in the Lixiana SPC.

The Panel noted the relevant information in Section 4.2 of the Lixiana SPC. The Panel considered that whether a special warning or precaution needed to be referred to in a particular section of material depended on a consideration of all of the circumstances including the nature of the warning/precaution, the therapy area and the content, layout and intended use of the material.

The Panel considered the immediate and overall impression to a busy health professional. In the Panel's view, the bold and prominent reference to 'renal impairment', which followed the statement 'Recommended for patients with one or more of the following factors that increases risks of bleeding' within a section titled '30mg Reduced dose' in bold font might have implied that the 30mg dosage was suitable in all stages of renal impairment which was not so. The reference to CrCl of 15-50ml/min below in less prominent font did not negate the misleading impression given that a 30mg dose could be used in all stages of renal impairment. In the Panel's view, the omission of the

information that any dose of edoxaban was not recommended in patients with end stage renal disease (CrCl < 15 mL/min) or on dialysis, within a section about dosing in renal impairment, was such that it was misleading and therefore breaches of the Code were ruled including that high standards had not been maintained.

Clause 2 was a sign of particular censure and was reserved for such use. The Panel noted that the creatine clearance value corresponding to moderate or severe renal impairment, which was the stage of renal impairment in which a reduced dose of 30mg was recommended, was given on the page, albeit in less prominent font. The Panel did not consider that a breach of Clause 2 was warranted in the particular circumstances of this case and no breach of Clause 2 was ruled.

5 Claims 'Lower incidence of major bleeding and major GI bleeding' and 'Lower incidence of stroke/SEE [systemic embolic events]'

The complainant alleged that the two claims were hanging comparisons as it did not say what Lixiana demonstrated these clinical endpoints against.

The Panel noted that the section at issue stated 'ETNA-AF supports the efficacy and safety profile of Lixiana in routine clinical practice', beneath which were the claims 'Lower incidence of major bleeding and major GI bleeding than in the pivotal phase 3 study' and 'Lower incidence of stroke/SEE than in the pivotal phase 3 study'. The Panel noted Daiichi-Sankyo's submission that the complainant had omitted the whole claims and that the comparison was between the ETNA-AF study and the pivotal phase 3 study. The Panel noted that the complainant bore the burden of proof and, in the Panel's view, he/she had not established that the two claims were hanging comparisons as alleged and no breach of the Code was ruled in relation to each.

6 Claim 'ETNA-AF supports the efficacy and safety profile of Lixiana in routine clinical practice'

The complainant alleged that once more the claim implied that Lixiana was safe in breach of the Code.

The Panel noted that the page referred to the safety profile of Lixiana and considered that there was a difference between a medicine being described as 'safe' and referring to its 'safety profile'. In the Panel's view, reference to the safety profile within the claim in question explained that the real world ETNA-AF data supported the safety profile of Lixiana in routine clinical practice and the findings of the pivotal Phase 3 study. The Panel did not consider that the complainant had established that the claim 'ETNA-AF supports the efficacy and safety profile of Lixiana in routine clinical practice' implied that Lixiana was safe as alleged. The Panel thus ruled no breaches of the Code including no breach of Clause 2.

7 Footnotes

The complainant alleged that the page had several footnotes, thereby bypassing qualification of huge content of information presented on the page.

The Panel noted that the complainant bore the burden of proof and did not consider, based on the allegation, that the complainant had established why the use of footnotes on the webpage in question was in breach of the Code and no breach of the Code was ruled.

8 'Contact us' page

The complainant alleged that the contact us page on the website (https://lixiana-hcp.co.uk/contact-us/ solicited medical information enquiries and these should always be unsolicited.

The Panel noted that whilst providing general contact details on a website was good practice, it considered that by inviting readers to contact the company for more information about Lixiana, Daiichi-Sankyo had solicited requests and therefore the responses given by the company in this regard would not be exempt from the definition of promotion. The Panel noted that the drop-down option stated 'Medical Information' and therefore the email would likely go to the medical information department who would, on the balance of probabilities, not treat its response as promotional material. However, the Panel had no information before it as to what, if any, questions were received via the website and whether such responses were treated as promotional or not. The Panel noted that the complainant bore the burden of proof and did not consider that he/she had established that Daiichi-Sankyo had breached the Code as alleged. The Panel therefore ruled no breach of the Code.

B My anticoagulant website (https://myanticoagulant.co.uk/ (Date of preparation: December 2020 – EDX/20/1264))

The complainant alleged that the landing page of the website had a brand name, generic name and indication which made it promotional. Therefore, it was inappropriate that there were no sections listed for a patient, member of the public or even the health professional. A member of the public would be promoted to, and certainly look to access the content and ask health professionals for the medicine, which would be inappropriate.

The complainant submitted that in addition, the landing page needed a link to prescribing information for health professionals but was not given.

The Panel noted Daiichi-Sankyo's submission that the myanticoagulant.co.uk landing page at issue was accessible via a link from the Lixiana.co.uk landing page, if the user confirmed he/she was not a health professional and confirmed that they were a patient taking Lixiana. The Panel further noted Daiichi-Sankyo's submission that the link to the page could also be found in patient support materials which were labelled as being for patients taking the medicine. The Panel did not have these patient support materials before it.

The Panel queried whether the full Lixiana indication was needed on the myanticoagulant.co.uk landing page; however, in order to get to this landing page, it appeared that the reader would have to select that they were a patient taking Lixiana from the Lixiana.co.uk landing page or would have accessed the page directly based on information in patient support materials given to them when they were prescribed Lixiana. The Panel noted Daiichi-Sankyo's submission that it did not publicise the

website through other routes and that the landing page clearly stated that it was for UK patients who had been prescribed Lixiana.

It was not clear to the Panel if the myanticoagulant.co.uk website could be easily found via an internet search if frequently used terms were entered into a search engine; Daiichi-Sankyo made no submission in that regard. On the evidence before it, the Panel considered that it appeared that the myanticoagulant.co.uk website, and therefore the landing page at issue, was directed to and signposted for individuals who had been prescribed Lixiana. The Panel therefore did not consider that the complainant had established that the myanticoagulant.co.uk landing page promoted a prescription only medicine to the public or would encourage members of the public to ask their health professionals for the medicine as alleged and no breaches of the Code were ruled including no breach of Clause 2 in that regard. Nor did the Panel consider that the complainant had established that the landing page in question promoted a prescription only medicine to health professionals and therefore no breaches of the Code were ruled including no breach of Clause 2 in that regard.

An anonymous complainant, who was originally contactable but later became non-contactable, complained about two Daiichi-Sankyo websites for Lixiana (edoxaban) (links were provided).

The complainant submitted that two standalone websites, for a product that could be dangerous to patients if used incorrectly, had multiple failings and errors which did not follow the principles of patient safety nor the Code of practice. The complainant referred to focussing on enhancing signatory knowledge. There had been multiple compliance failings over promotion of edoxaban over the years and yet it was the same case once more here. The complainant requested that the PMCPA look more closely at the practices of Daiichi-Sankyo in the promotion of Lixiana.

Lixiana was indicated, among other things, in 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).

A Lixiana website (https://lixiana-hcp.co.uk/)

1 Claims 'Your choice for ageing patients with NVAF' and 'Real-world evidence reinforces Lixiana as your DOAC [direct oral anticoagulant] of choice for ageing patients with NVAF[1,2]'

COMPLAINT

The complainant alleged that the headline claim, 'your choice for ageing patients with NVAF [non-valvular atrial fibrillation]' right at the start of the page (https://lixiana-hcp.co.uk/ (ref EDX/21/0176, Date of preparation March 2021)) was misleading and could not be substantiated as Lixiana was only licensed for an age group of ≥75 years in patients with NVAF. It was not appropriate to use such a broad claim in reference to ageing as this could be subjective to health professionals' interpretation, for example, a 60 year old with NVAF could be seen as ageing but was not suitable for Lixiana treatment. The complainant alleged breaches of Clauses 7.2, 7.4, 9.1 and 2 of the Code.

The complainant alleged that another page of the same website https://lixiana-hcp.co.uk/etna-af-europe/ (ref EDX/20/1123, Date of preparation December 2020), again made the headline claim 'Real-world evidence reinforces Lixiana as your DOAC of choice for ageing patients with NVAF[1,2]'. There was no mention of age groups in reference to what the licence was. It was pivotal to note that health professionals could access any page in isolation, so all pages needed to standalone. This was again a breach of the same clauses as stated above for the homepage.

RESPONSE

Daiichi-Sankyo submitted that the complainant was incorrect that Lixiana was 'only licensed for an age group of ≥75 years in patients with NVAF'. The section directly underneath the headline on the page (https://lixiana-hcp.co.uk/ (ref EDX/21/0176, Date of preparation March 2021) detailed 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 that 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 explained that as patients with NVAF aged, they developed more comorbidities and risk factors which put them at increased risk of stroke and systemic embolism; these were not misleading claims (no breach of Clause 7.2) or claims that were incapable of substantiation (no breach of Clause 7.4). Therefore, 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).

PANEL RULING

The Panel noted that 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)'. The Panel noted Daiichi-Sankyo's submission that as patients with NVAF aged, they developed more comorbidities and risk factors which put them at increased risk of stroke and systemic embolism.

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 use of the wording 'such as' indicated that the list of risk factors was not exhaustive and only one risk factor was required to be eligible for Lixiana, which did not necessarily have to be age ≥75 years. The Panel did not consider that the complainant had established that the claims in question were misleading or incapable of substantiation as alleged and, based on the complainant's narrow allegation, no breach of Clauses 7.2 and 7.4 were ruled in relation to each claim. The Panel consequently ruled no breach of Clauses 9.1 and 2 in relation to each claim.

2 Claim 'Efficacy and safety profile even when used with appropriate dose reduction'

COMPLAINT

The complainant submitted that there was a section further down on the webpage which read 'What is Lixiana indicated for'. Underneath the indication, there were three claims, one which read 'Efficacy and safety profile even when used with appropriate dose reduction'. By stating safety profile within dose reduction, this implied that Lixiana was safe and did not have side effects even when dosage was reduced. The complainant alleged that this was inappropriate and was in breach of Clause 7.9. Lixiana could be fatal with some side effects and the complainant alleged that to downgrade the safety implications with such a claim put patient safety at risk in breach of Clause 9.1 and Clause 2.

RESPONSE

Daiichi-Sankyo submitted that this statement meant that the efficacy and safety profile for edoxaban had been investigated at the standard dose as well as with an appropriately reduced dose. No claim was made here as to what that efficacy and safety profile was, it was just a statement to enable the reader to be aware that there was efficacy and safety data available in patients who had appropriate dose reduction. There was no claim that edoxaban was 'safe'. The next section directly underneath did go into detail about what that safety data was and stated 'Lixiana demonstrated superior reduction in major bleeding vs well-managed warfarin. In the safety-on-treatment population the annualised rate of major bleeding events with once-daily Lixiana vs well-controlled warfarin was: 2.75% vs 3.43%. HR 0.80; 95% CI, 0.71 to 0.91; P<0.001'. This result of the ENGAGE study's principal safety endpoint included patients on the standard dose and those who had been appropriately dose reduced. Daiichi-Sankyo submitted that it had not implied that Lixiana was safe or that it did not have side effects when dosage was reduced (no breach of Clause 7.9). Daiichi-Sankyo had merely stated that a safety profile existed and had then gone into detail about that safety profile. Therefore, 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).

PANEL RULING

The Panel noted the complainant's allegation that the claim implied that Lixiana was safe and did not have side effects even when dosage was reduced. The Panel noted Daiichi-Sankyo's submission that the claim 'Efficacy and safety profile even when used with appropriate dose reduction' was intended to convey that the efficacy and safety profile for edoxaban had been investigated at the standard dose as well as with an appropriately reduced dose and that no claim was made as to what that efficacy and safety profile was. The Panel considered that there was a difference between a medicine being described as 'safe' and referring to the 'safety profile' of a medicine. In the Panel's view, it was not unacceptable to refer to a medicine's safety profile which would likely be interpreted as there being safety information available about the medicine. The Panel considered that, although the claim was somewhat ambiguous, the complainant had not established that it implied that Lixiana was safe and lacked side effects as alleged and therefore no breach of Clause 7.9 was ruled. The Panel consequently ruled no breach of Clauses 9.1 and 2.

3 Claim 'Lactose not listed as an excipient'

COMPLAINT

The complainant submitted that further down on the same page, there was another claim, 'Lixiana – simple and convenient once-daily dosing in NVAF' and below this to the side was the

claim 'Lactose not listed as an excipient'. The complainant alleged that this again put patient safety at risk as Daiichi-Sankyo could not guarantee that there had been no contact with lactose during manufacture. This would be a major risk for patients with lactose intolerance as they could have anaphylaxis to lactose. Ironically, this extra information about lactose being in potential contact during manufacture was right at the bottom of the page, presented as a footnote. The claim that lactose was not an excipient should have had this important wording around contact during manufacture directly below or adjacent to the claim about lactose as an excipient as opposed to hidden as a footnote. The complainant alleged breaches of Clauses 7.2, 9.1 and 2.

RESPONSE

Daiichi-Sankyo noted that the complainant had not made a specific allegation about the claim 'Lixiana – simple and convenient once-daily dosing in NVAF' and so it provided no further comment in that regard.

Daiichi-Sankyo submitted that lactose was often included as an excipient in medicinal products and the company was frequently asked if its products contained it. Lactose was not listed as an excipient in the Lixiana SPC and was not expected to be present in the product and so the claim, 'Lactose not listed as an excipient' was accurate and not misleading (no breach of Clause 7.2). Out of an abundance of caution, a footnote additionally stated that the company could not guarantee that there had been no contact with lactose during manufacture. Therefore, 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).

PANEL RULING

The Panel noted that the claim 'Lactose not listed as an excipient[#]' appeared in bold typeface under the section 'Lixiana – simple and convenient once-daily dosing in NVAF[5]', alongside an icon of what appeared to be a milk carton which had '0%' on it. The Panel noted that the reader was directed to a footnote that was not in bold typeface and appeared near the end of the page towards the bottom of a list of footnotes and stated: 'We cannot guarantee that there has been no contact with lactose during manufacture. Use with caution in patients that have had severe anaphylaxis with lactose products'. The caution was referenced to a poster by De Groot JR *et al* presented at ESC 2019. The Panel did not have a copy of this poster and Daiichi-Sankyo made no submission in this regard.

Clause 7.2 stated, *inter alia*, that information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication, by distortion, exaggeration or undue emphasis. The supplementary information to Clause 7 required that claims in promotional material must be capable of standing alone as regards accuracy etc. In general, claims should not be qualified by the use of footnotes and the like.

The Panel considered the immediate and overall impression to a busy health professional and in the Panel's view the claim was misleading. Whilst the Panel noted that lactose was not listed as an excipient in the Lixiana SPC, when the claim was read in isolation without the footnote, the proactive provision of the statement 'lactose not listed as an excipient', alongside the icon of a milk carton which had 0% on it, implied that there would be no concerns using Lixiana in

patients with a lactose allergy which was not so; according to the footnote, there was no guarantee that there had been no contact with lactose during manufacture and there was a caveat to use Lixiana with caution in patients that have had severe anaphylaxis with lactose products. The Panel considered that a busy health professional might not have read the important information in the footnote which should have appeared immediately alongside, and with equal prominence to, the claim in question. The Panel therefore ruled a breach of Clause 7.2. The Panel considered that Daiichi-Sankyo had failed to maintain high standards in this regard and a breach of Clause 9.1 was ruled.

Clause 2 was a sign of particular censure and was reserved for such use. The Panel noted Daiichi-Sankyo's submission that lactose was not listed as an excipient in the Lixiana SPC and was not expected to be present in Lixiana but it had included the footnote out of an abundance of caution. The Panel noted its rulings of breaches of the Code above and considered that, on balance, these adequately covered the matter; in the Panel's view, a breach of Clause 2 was not warranted in the particular circumstances of this case and, on balance, no breach of Clause 2 was ruled.

4 Claim relating to using 30mg of edoxaban in certain circumstances which mentioned low renal function of creatinine clearance between 15-50ml/min

COMPLAINT

The complainant noted that the claim, again on the same page as the claim at issue in Point 3, related to using 30mg of edoxaban in certain circumstances which mentioned low renal function of creatinine clearance between 15-50ml/min. However, in patients with end stage renal disease or on dialysis, Lixiana was not recommended (the complainant referred to Sections 4.2 and 5.2 of the SPC). That information should have been provided as a busy health professional reading the page or someone not experienced with Lixiana usage could interpret the claim in a misleading fashion. Information should always be fair and balanced and should not have been omitted by only mentioning a certain renal function which suited Daiichi-Sankyo. The complainant alleged breaches of Clauses 7.2, 9.1 and 2.

RESPONSE

Daiichi-Sankyo submitted that this was a section on the appropriate dose reduction criteria where patients should take 30mg instead of 60mg. The SPC stated:

'For NVAF and VTE [venous thromboembolism] 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.'

The dose reduction criteria from the SPC was captured in the section described by the complainant. A dose of 30mg would be appropriate in patients with CrCl 15-50ml/min. There was no suggestion that edoxaban should be used in patients with CrCl below 15ml/min (which would include patients with end stage renal disease or on dialysis). This claim was not misleading (no breach of Clause 7.2). Therefore, 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). (Copies of the two screen shots were provided).

PANEL RULING

The Panel noted that under the heading 'Lixiana – simple and convenient once-daily dosing in NVAF' beneath a subheading in bold font '30mg Reduced dose', it referred to a dose of 30mg once daily in patients with one or more factors that increased the risk of bleeding including, *inter alia*, renal impairment, which appeared in bold font next to an image of the kidneys. CrCl 15-50ml/min appeared below in less prominent font. The Panel noted that CrCl 15-50ml/min was described as moderate or severe renal impairment in the Lixiana SPC.

The Panel noted that Section 4.2 of the Lixiana SPC stated that for 'NVAF and VTE the recommended dose was 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'.

Section 4.2 of the SPC further stated under the heading 'Renal impairment' that renal function should be assessed in all patients by calculating the CrCl prior to initiation of treatment with edoxaban to exclude patients with end stage renal disease (i.e. CrCl < 15 mL/min), to use the correct edoxaban dose in patients with CrCl 15 – 50 mL/min (30 mg once daily), in patients with CrCl > 50 mL/min (60 mg once daily) and when deciding on the use of edoxaban in patients with increased CrCl (see section 4.4). Section 4.2 of the SPC also stated that in patients with end stage renal disease (ESRD) (CrCl < 15 mL/min) or on dialysis, the use of edoxaban is not recommended (see sections 4.4 [Special warnings and precautions for use] and 5.2 [Pharmacokinetic properties]). The Panel noted Daiichi-Sankyo's submission that there was no suggestion in the material at issue that edoxaban could be used in patients with CrCl below 15ml/min which would include patients with end stage renal disease or on dialysis.

The Panel considered that whether a special warning or precaution needed to be referred to in a particular section of material depended on a consideration of all of the circumstances including the nature of the warning/precaution, the therapy area and the content, layout and intended use of the material.

The Panel considered the immediate and overall impression to a busy health professional. In the Panel's view, the bold and prominent reference to 'renal impairment', which followed the statement 'Recommended for patients with one or more of the following factors that increases risks of bleeding' within a section titled '30mg Reduced dose' in bold font might have implied that the 30mg dosage was suitable in all stages of renal impairment which was not so. The reference to CrCl of 15-50ml/min below in less prominent font did not negate the misleading impression given that a 30mg dose could be used in all stages of renal impairment. In the Panel's view, the omission of the information that any dose of edoxaban was not recommended in patients with end stage renal disease (CrCl < 15 mL/min) or on dialysis, within a section about dosing in renal impairment, was such that it was misleading and therefore a breach of Clause 7.2 was ruled. High standards had not been maintained in this regard and a breach of Clause 9.1 was ruled.

Clause 2 was a sign of particular censure and was reserved for such use. The Panel noted that the creatine clearance value corresponding to moderate or severe renal impairment, which was

the stage of renal impairment in which a reduced dose of 30mg was recommended, was given on the page, albeit in less prominent font. The Panel did not consider that a breach of Clause 2 was warranted in the particular circumstances of this case and no breach of Clause 2 was ruled.

5 Claims 'Lower incidence of major bleeding and major GI bleeding' and **'Lower incidence of stroke/SEE [systemic embolic events]'**

COMPLAINT

The complainant noted that on the website https://lixiana-hcp.co.uk/etna-af-europe/ there were two claims further down the page 'Lower incidence of major bleeding and major GI bleeding' and 'Lower incidence of stroke/SEE [systemic embolic events]'. The complainant alleged that this was a hanging comparison as it did not say what Lixiana demonstrated these clinical endpoints against. The complainant alleged that both claims breached Clause 7.2.

RESPONSE

Daiichi-Sankyo submitted that in both these cases, the complainant had omitted the whole claim and that the comparison was clearly regarding the ETNA-AF study vs the pivotal phase 3 study. The statement directly above stated 'ETNA-AF supports the efficacy and safety profile of Lixiana in routine clinical practice'. The full claims in question directly underneath then stated 'Lower incidence of major bleeding and major GI bleeding than in the pivotal phase 3 study' and 'Lower incidence of stroke/SEE than in the pivotal phase 3 study'. Daiichi-Sankyo submitted that there was no hanging comparison and hence no breach of Clause 7.2 (a copy of the screenshot was provided).

PANEL RULING

The Panel noted that the section at issue stated 'ETNA-AF supports the efficacy and safety profile of Lixiana in routine clinical practice', beneath which were the claims 'Lower incidence of major bleeding and major GI bleeding than in the pivotal phase 3 study' and 'Lower incidence of stroke/SEE than in the pivotal phase 3 study'. The Panel noted Daiichi-Sankyo's submission that the complainant had omitted the whole claims and that the comparison was between the ETNA-AF study and the pivotal phase 3 study. The Panel noted that the complainant bore the burden of proof and, in the Panel's view, he/she had not established that the two claims were hanging comparisons as alleged and no breach of Clause 7.2 was ruled in relation to each.

6 Claim 'ETNA-AF supports the efficacy and safety profile of Lixiana in routine clinical practice'

COMPLAINT

The complainant alleged that once more the claim implied that Lixiana was safe in breach of Clauses 7.9, 9.1 and 2.

RESPONSE

Daiichi-Sankyo submitted that the claim did not state that edoxaban was 'safe', it meant that that the real world ETNA-AF data supported the established efficacy and safety profiles. This was further detailed directly below: 'Lower incidence of major bleeding and major GI bleeding than in

the pivotal phase 3 study'. Therefore, there was no breach of Clause 7.9. There was thus 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) (a copy of the screenshot was provided).

PANEL RULING

The Panel noted that the page referred to the safety profile of Lixiana and considered that there was a difference between a medicine being described as 'safe' and referring to its 'safety profile'. In the Panel's view, reference to the safety profile within the claim in question explained that the real world ETNA-AF data supported the safety profile of Lixiana in routine clinical practice and the findings of the pivotal Phase 3 study. The Panel did not consider that the complainant had established that the claim 'ETNA-AF supports the efficacy and safety profile of Lixiana in routine clinical practice' implied that Lixiana was safe as alleged. The Panel thus ruled no breach of Clause 7.9. The Panel consequently ruled no breach of Clauses 9.1 and 2.

7 Footnotes

COMPLAINT

The complainant alleged that the page had several footnotes, thereby bypassing qualification of huge content of information presented on the page, in breach of Clause 9.1.

RESPONSE

Daiichi-Sankyo noted that the complainant had not clarified any specific concerns. The footnotes enabled the health professional to find out more information should they choose to do so, but the claims in the main body of the page stood alone. Daiichi-Sankyo denied a breach of Clause 9.1.

PANEL RULING

The Panel noted that the complainant was concerned with the use of footnotes in general on the page at issue but had provided no reasons to support why in his/her view the use of footnotes *per se* was a breach of the Code. It was not for the Panel to make out a complainant's case. The Panel noted that the complainant bore the burden of proof and did not consider, based on the allegation, that the complainant had established why the use of footnotes on the webpage in question was in breach of the Code and no breach of Clause 9.1 was ruled.

8 'Contact us' page

COMPLAINT

The complainant alleged that the contact us page on the website (https://lixiana-hcp.co.uk/contact-us/ (Date of preparation: December 2020 EDX/20/1121)) solicited medical information enquiries. Medical information enquiries should always be unsolicited. The complainant alleged a breach of Clause 9.1.

RESPONSE

Daiichi-Sankyo submitted that the page provided an avenue for health professionals to contact the company if they needed to. It did not solicit enquiries. The page stated:

> 'If you have any medical information queries about Lixiana, please contact us using the form below selecting the "medical queries" option.
>
> Daiichi-Sankyo values your feedback. Please send us your comments or queries using the contact form below. We will only use your details to reply to your specific request and will not use your details for any other purpose.
>
> Adverse events should be reported. Reporting forms and information can be found at: www.mhra.gov.uk/yellowcard.
>
> Adverse events should also be reported to Daiichi-Sankyo UK pharmacovigilance on: 0800 028 5122 or pharmacovigilance@daiichi-sankyo.co.uk.'

The form presented three items from a drop-down menu that could be selected, Medical Information, Patient Materials, General Enquiries, each of which would be directed to the appropriate member of staff responsible for dealing with each category of query. Daiichi-Sankyo denied a breach of Clause 9.1 (a copy of the screenshot was provided).

PANEL RULING

The Panel noted that Clause 1.2 of the Code stated, *inter alia*, that replies made in response to individual enquiries from members of the health professions or other relevant decision makers were exempt from the definition of promotion only if they related solely to the subject matter of the enquiry, were accurate and did not mislead and were not promotional in nature. The supplementary information to this clause stated that the exemption related to unsolicited enquiries only, which were those without any prompting from the company. The supplementary information further stated that a solicited enquiry would be one where a company invited a person to make a request, for example, material offering further information to readers would be soliciting a request for that information.

The Panel noted that whilst providing general contact details on a website was good practice, it considered that by inviting readers to contact the company for more information about Lixiana, Daiichi-Sankyo had solicited requests and therefore the responses given by the company in this regard would not be exempt from the definition of promotion. The Panel noted that the drop-down option stated 'Medical Information' and therefore the email would likely go to the medical information department who would, on the balance of probabilities, not treat its response as promotional material. However, the Panel had no information before it as to what, if any, questions were received via the website and whether such responses were treated as promotional or not. The Panel noted that the complainant bore the burden of proof and did not consider that he/she had established that Daiichi-Sankyo had breached the Code as alleged. The Panel therefore ruled no breach of Clause 9.1.

B My anticoagulant website (https://myanticoagulant.co.uk/ (Date of preparation: December 2020 – EDX/20/1264))

COMPLAINT

The complainant noted that the home (landing page) of the website had a brand name, generic name and indication. That made it a promotional landing page without doubt. Therefore, it was inappropriate that there were no sections listed for a patient, member of the public or even the health professional. A member of the public would be promoted to, and certainly look to access the content and ask health professionals for the medicine, which would be inappropriate. The complainant alleged breaches of Clauses 26.1, 26.2, 28.1, 9.1 and 2.

The complainant alleged that in addition, this was a promotional landing page due to brand name and indication, thereby needing a link to prescribing information for health professionals but this was not given. This was a breach of Clauses 4.1, 14.1 (as it was evident promotional certification missed these basics), 9.1 and 2.

RESPONSE

Daiichi-Sankyo submitted that the page was accessible via a link from the Lixiana.co.uk landing page, if the user confirmed he/she was not a health professional and that they were a patient taking Lixiana. Alternatively, the link to the page was found in patient support materials which were clearly labelled as being intended for patients taking the medicine. Therefore, nobody would find the landing page in question if they were not a patient. Daiichi-Sankyo did not publicise the page through other routes. The page itself clearly stated it was intended for patients taking the medicine. On that basis, it was not promoting to the public (no breach of Clause 26.1). There was nothing to encourage members of the public to ask for a prescription as the audience would already be patients (no breach of Clause 26.2). This was not promotion (no breach of Clause 28.1); breaches of Clauses 9.1 or 2 were also denied.

Daiichi-Sankyo submitted that as the website was not promotional it denied breaches of Clauses 4.1, 14.1, 9.1 and 2 respectively.

PANEL RULING

The Panel noted Daiichi-Sankyo's submission that the myanticoagulant.co.uk landing page at issue was accessible via a link from the Lixiana.co.uk landing page, if the user confirmed he/she was not a health professional and confirmed that they were a patient taking Lixiana. The Panel further noted Daiichi-Sankyo's submission that the link to the page could also be found in patient support materials which were labelled as being for patients taking the medicine. The Panel did not have these patient support materials before it.

The Panel queried whether the full Lixiana indication was needed on the myanticoagulant.co.uk landing page; however, in order to get to this landing page, it appeared that the reader would have to select that they were a patient taking Lixiana from the Lixiana.co.uk landing page or would have accessed the page directly based on information in patient support materials given to them when they were prescribed Lixiana. The Panel noted Daiichi-Sankyo's submission that it did not publicise the website through other routes and that the landing page clearly stated that it was for UK patients who had been prescribed Lixiana.

It was not clear to the Panel if the myanticoagulant.co.uk website could be easily found via an internet search if frequently used terms were entered into a search engine; Daiichi-Sankyo made no submission in that regard. On the evidence before it, the Panel considered that it appeared that the myanticoagulant.co.uk website, and therefore the landing page at issue, was directed to and signposted for individuals who had been prescribed Lixiana. The Panel

therefore did not consider that the complainant had established that the myanticoagulant.co.uk landing page promoted a prescription only medicine to the public or would encourage members of the public to ask their health professionals for the medicine as alleged and no breach of Clauses 26.1, 26.2 and 28.1 were ruled. The Panel consequently ruled no breach of Clauses 9.1 and 2 in that regard. Nor did the Panel consider that the complainant had established that the landing page in question promoted a prescription only medicine to health professionals and therefore no breach of Clauses 4.1 and 14.1 were ruled. The Panel consequently ruled no breach of Clauses 9.1 and 2 in that regard.

Complaint received **27 March 2021**

Case completed **16 December 2021**