CASE AUTH/3634/4/22 ***NO BREACH OF THE CODE***

COMPLAINANT v DAIICHI SANKYO

Allegations about an Edoxaban leavepiece

CASE SUMMARY

This case was in relation to a promotional leavepiece on how to initiate Lixiana (edoxaban).

Whilst the Panel had some concerns about the material, it ruled no breach of the following Clauses of the 2021 Code on the very narrow point that there was no evidence that it had been made available in any format to health professionals on or before the date of the complaint and the complainant had not established that relevant personnel had not been trained or were not conversant with the Code:

No Breach of Clause 6.1	**Requirement that information must be accurate, up-to-date and not misleading**
No Breach of Clause 6.2	**Requirement that claims/information/comparisons must be capable of substantiation**
No Breach of Clause 9.1	**Requirement that all relevant personnel must be fully conversant with the Code**
No Breach of Clause 2	**Requirement that activities or material must not bring discredit upon, or reduce confidence in, the pharmaceutical industry**

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

FULL CASE REPORT

A complainant, who described him/herself as a cardiac specialist, complained about a promotional leavepiece created by Daiichi Sankyo for UK prescribers on how to initiate Lixiana (edoxaban). In his/her previous complaint (Case AUTH/3632/4/22), he/she had mentioned the importance of hepatic function monitoring pre and post initiation of edoxaban.

COMPLAINT

The complainant stated that the leavepiece at issue was titled 'edoxaban leavepiece' and could be downloaded from a webpage for which a link was provided. The complainant also provided a direct link to the PDF leavepiece (EDX/22/0161 Date of preparation: March 2022). The complainant alleged that the leavepiece had guidance on initiating edoxaban but only discussed renal function and not hepatic function. This was allegedly a major risk for patients especially those who were older age with reduced liver function. The complainant stated that the summary

of product characteristics (SPC) mentioned the following important information with regard to hepatic function:

> 'Edoxaban was contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 4.3). In patients with severe hepatic impairment edoxaban was not recommended (see sections 4.4 and 5.2). In patients with mild to moderate hepatic impairment the recommended dose was 60 mg edoxaban once daily (see section 5.2). Edoxaban should be used with caution in patients with mild to moderate hepatic impairment (see section 4.4). Patients with elevated liver enzymes (alanine aminotransferase (ALT) or aspartate transaminase (AST) > 2 x upper limit of normal (ULN)) or total bilirubin ≥ 1.5 x ULN, were excluded in clinical studies. Therefore, edoxaban should be used with caution in this population (see sections 4.4 and 5.2). Prior to initiating edoxaban, liver function testing should be performed.'

The complainant alleged that the omission of hepatic information meant that the leavepiece was not accurate, not balanced and posed a safety challenge to prescribers as there was no information on hepatic considerations. The complainant stated it was bizarre that all stages of renal impairment information had been given within the leavepiece but nothing on hepatic impairment and this was allegedly a reckless omission and brought discredit to the industry in breach of Clauses 6.1, 6.2, 9.1 and 2.

When writing to Daiichi Sankyo, the Authority asked it to consider the requirements of Clauses 2, 6.1, 6.2 and 9.1 of the 2021 Code.

RESPONSE

Daiichi Sankyo UK stated that it took its obligations under the Code seriously and strove to maintain high standards and to behave responsibly and ethically at all times.

Daiichi Sankyo denied breaches of Clauses 6.1, 6.2, 9.1 and 2 of the Code.

Daiichi Sankyo submitted that it was not clear why the complainant had alleged a breach of Clause 9.1 but as training had not been mentioned, Daiichi Sankyo denied a breach of Clause 9.1.

Daiichi Sankyo submitted that the leavepiece was designed upon request from a health professional representing a learned society who provided input into the content of the leavepiece. The health professional specifically wanted to address dosing with edoxaban and renal function, and to demonstrate how to initiate edoxaban and how to dose reduce safely. According to the contracted health professional, up to 40% of patients in the UK were prescribed the incorrect dose of a DOAC (Direct-acting oral anticoagulant) and therefore, the focus of this leavepiece was to educate clinicians regarding how to dose the patient correctly and according to what criteria in order to improve safety for patients.

Daiichi Sankyo submitted that following the link provided by the complainant, the item in question could be seen, and the first line read – '**Prescribing information and adverse event reporting for LIXIANA can be found on page 2 / reverse of this document. Please refer to the full summary of product characteristics before prescribing**'. Daiichi Sankyo submitted that it was here, under special warnings and precautions for use, that the full information

regarding Hepatic impairment and the need to perform a liver function test prior to initiation was outlined.

Daiichi Sankyo submitted that the leavepiece was designed in partnership with a learned society, to be hosted on the learned society's website designed specifically for health professional education. Daiichi Sankyo contracted committee members of the learned society who were cardiac health professional experts in their field, to create and deliver educational 'Talking Head' videos for health professionals in England, in order to address frequent questions about edoxaban and the NHSE&I commissioning recommendations. The intention of the leavepiece was to be an additional item to support the educational videos to enable health professionals to safely prescribe edoxaban to clinically appropriate patients.

Daiichi Sankyo submitted that the webpage hosting the leavepiece in question was not certified and not ready for distribution at the time of the complaint, therefore the leavepiece was not promoted by Daiichi Sankyo. The website provided by the complainant was an unlisted staging site provided by the learned society and used for testing purposes, which was not shared with, nor promoted to, health professionals or anyone else beyond the development and review teams. There was no link to the staging site from the learned society website already in use. Daiichi Sankyo and the learned society had validated this. It was unclear to Daiichi Sankyo how this was allegedly promoted as the complainant had not provided evidence of promotion, and the learned society had confirmed that there was no active promotion of it.

Daiichi Sankyo submitted that review of materials was part of the certification process to ensure alignment with the Code, and it ensured that any complaints were considered as part of the standard development and approval process of promotional materials. Additionally, the materials were developed in consultation with multidisciplinary cardiac health professional experts and included information necessary for the prescribing of edoxaban. Any amends to items were actioned as part of the development and certification process before promotion to health professionals, and before going live, to ensure accurate, fair, and balanced promotion.

Daiichi Sankyo submitted that the prescribing information was located at the end of the promotional leavepiece, and there was a clear and prominent statement at the top of the leavepiece to refer to prescribing information and the full SPC before initiating and prescribing edoxaban.

Daiichi Sankyo denied a breach of Clauses 6.1, 6.2, 9.1 and 2.

In conclusion, Daiichi Sankyo stated that it had acted in line with the requirements of the Code, maintained high standards and had not brought discredit upon, or reduced confidence in, the industry.

In response to a request for further information from the Panel, which had noted that the leavepiece at issue (EDX/22/0161) had been certified on 4 April 2022, Daiichi Sankyo submitted that the leavepiece was not used or distributed to health professionals before the date of the complaint (15 April 2022). It was rolled out to the field force in May 2022.

PANEL RULING

The Panel noted that the complainant referred to a promotional Lixiana (edoxaban) leavepiece and provided a link to a webpage on which the material was hosted along with a direct link to the material itself.

The complainant had not provided any evidence to show how the webpage hosting the leavepiece had been accessed from publicly available webpages. The Panel noted Daiichi Sankyo's submission that the webpage in question was not certified and not ready for distribution at the time of this complaint and therefore the leavepiece was not promoted by Daiichi Sankyo; the website provided by the complainant was an unlisted staging site provided by the learned society and used for testing purposes, which was not shared with, nor promoted to, health professionals or anyone else beyond the development and review teams. According to Daiichi Sankyo, there was no link to the staging site from the learned society website that was already in use and this had been validated by both Daiichi Sankyo and the learned society.

The Panel noted that the leavepiece in question was certified on 4 April 2022, prior to the Authority's receipt of this complaint. The Panel further noted Daiichi Sankyo's submission that the leavepiece was not used or distributed to health professionals before the date the complaint was made to the Authority (15 April 2022).

The Panel noted from Daiichi Sankyo's submission that the leavepiece was designed in partnership with the learned society to address dosing with edoxaban and renal function. The two-page leavepiece presented information about prescribing Lixiana and renal function dosing considerations on the first page and had Lixiana prescribing information on the second page. The first page, beneath the heading, 'NHS England and NHS Improvement (NHSE&I) recommend LIXIANA® (edoxaban) as the first choice DOAC for patients with NVAF where clinically appropriate' featured three highlighted boxes in relation to prescribing edoxaban: patients who were newly diagnosed with NVAF, transitioning from VKA or transitioning from another DOAC. The Panel noted that immediately below these three boxes was another highlighted box titled 'Renal function dosing considerations' which detailed dosing based on CrCl. The very top of the leavepiece referred the reader to the prescribing information and adverse event reporting on page 2/reverse of the document and an instruction to refer to the full SPC before prescribing.

The Panel noted the allegation that the omission of hepatic information meant this leavepiece was not accurate, not balanced and posed a safety challenge to prescribers. It appeared that the allegation was not in relation to the prescribing information (page 2) but the body of the leavepiece (page 1).

The Panel considered that whether a contraindication or special warning or precaution needed to be highlighted within a particular section of promotional material, in addition to its requirement to be included within the prescribing information that was required on all promotional material, depended on a consideration of all of the circumstances, including the nature of the contraindication/warning/precaution and the content, layout, audience and intended use of the material.

The Panel noted the hepatic considerations for edoxaban in its SPC included that it was not recommended in patients with severe hepatic impairment and that it should be used with caution in patients with mild to moderate hepatic impairment. The Panel further noted that the SPC stated that liver function testing should be performed prior to initiating edoxaban and that periodic hepatic monitoring was recommended beyond one year.

Noting Daiichi Sankyo's submission that the intention of this leavepiece was to be an additional item to support the educational videos to enable health professionals to safely prescribe edoxaban to clinically appropriate patients, the Panel was concerned about the omission of the hepatic considerations of edoxaban in the body of the leavepiece. In the Panel's view, it might be relevant to include such information in the body of material that was intended to advise health professionals on appropriate prescribing of the medicine.

Nonetheless, the Panel noted that the leavepiece had not been distributed or made available to health professionals at the time of the complaint. Whilst the Panel had some concerns about the certified material, there was no evidence that it had been made available in any format to health professionals on or before the date of the complaint and, on this very narrow point**,** the Panel ruled **no breaches of Clauses 6.1 and 6.2.**

The Panel noted that the complainant had raised Clause 9.1 which related to training in the 2021 Code. The Panel queried whether the complainant had intended to raise Clause 5.1 'High standards must be maintained at all times'.

Clause 9.1 of the 2021 Code stated that all relevant personnel, including members of staff and others retained by way of contract, concerned in any way with the preparation or approval of material or activities covered by the Code, must be fully conversant with the Code and the relevant laws and regulations. Whilst the Panel had some concerns about the certified material, the complainant had not established that relevant personnel had not been trained or were not conversant with the Code and **no breach of Clause 9.1** was ruled in that regard.

The Panel noted its rulings of no breaches of the Code above and subsequently ruled **no breach of Clause 2.**

Complaint received **15 April 2022**

Case completed **3 April 2023**