CASE AUTH/3627/4/22

COMPLAINANT v DAIICHI SANKYO

Allegations about Lixiana patient booklets

CASE SUMMARY

This case was in relation to two booklets created by Daiichi Sankyo for patients prescribed Lixiana (edoxaban).

Whilst the front page of each booklet stated, 'It's important to read the Lixiana package leaflet provided with your medicine', the Panel considered that it might not be clear to all patients that each 20 page booklet was not a substitute for the package leaflet or that the package leaflet contained additional important information on the use of the medicine that was not in the booklet.

The Panel ruled a breach of the following Clauses of the 2021 Code in relation to each booklet for the omission of safety information (exceptional weakness, tiredness, paleness, dizziness, headache or unexplained swelling) which, in the Panel's view, might not be readily recognised as signs of excessive bleeding by the patient, and the misleading impression given that each booklet contained all the relevant information that the patient needed in relation to bleeding, which was incapable of substantiation and might prejudice patient safety:

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	**Misleading impression incapable of substantiation**

The Panel ruled no breach of the following Clause of the 2021 Code in relation to each booklet as it did not consider that either booklet implied that the medicine had no side effects or no bleeding risk:

No Breach of Clause 6.4	**Requirement that it must not be stated that a product has no adverse reactions**

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

FULL CASE REPORT

A contactable complainant who described him/herself as a health professional complained about two booklets for patients prescribed Lixiana (edoxaban) produced by Daiichi Sankyo. The first was titled 'Understanding your treatment for atrial fibrillation' and the second 'Understanding your treatment for venous thromboembolism'.

COMPLAINT

The complainant alleged that the two patient booklets were missing important safety information that was in the Lixiana patient information leaflet (PIL) side effects section but not in the 2 booklets produced by Daiichi Sankyo.

The first booklet (EDX/21/0229, March 2021) was for patients prescribed Lixiana for atrial fibrillation and the second booklet was for patients who were prescribed Lixiana for venous thromboembolism (EDX/20/1071, December 2020). Both booklets included a page headed 'What about potential side effects?' (Page 16). The complainant alleged that this section in each was missing important patient safety information from section 4 of the PIL, which stated, under possible side effects:

> 'If you experience any bleeding event that does not stop by itself or if you experience signs of excessive bleeding (exceptional weakness, tiredness, paleness, dizziness, headache or unexplained swelling) consult your doctor immediately. Your doctor may decide to keep you under closer observation or change your medicine'.

The complainant alleged that none of this important information that a patient needed to know was included on page 16 or anywhere else within each booklet. This complainant considered that this was a patient safety risk and breaches of Clauses 6.1, 6.2, 6.4, 5.1 and 2 were alleged in relation to each booklet.

The complainant stated that as this information was related to patient safety, there needed to be a corrective statement to health professionals that the booklets had been provided to as the health professionals were providing these to patients who would use the booklet as a main source of information.

When writing to Daiichi Sankyo, the Authority asked it to consider the requirements of Clauses 6.1, 6.2, 6.4, 5.1 and 2 of the 2021 Code as cited by the complainant.

RESPONSE

Daiichi Sankyo stated that it took its obligations under the Code seriously, and strove to maintain high standards and behave responsibly and ethically at all times. The company denied all alleged breaches.

Atrial Fibrillation booklet

Daiichi Sankyo submitted that there was no requirement in the Code that information provided to patients in a PIL must be provided verbatim in company-produced material intended for patient support. Nevertheless, in the document in question (EDX/21/0229) the opening page it stated in

bold typeface '**It's important to read the Lixiana package leaflet provided with your medicine'** underneath the adverse event reporting statement. Moreover, this was bookended on page 16 with the additional statement, again in bold typeface:

> '**Bleeding is not always obvious. If you experience any side effects, talk to your doctor or pharmacist. It is important not to stop taking Lixiana without talking to them first**'

and

> **'Please refer to package leaflet for further information about adverse effects.'**

Daiichi Sankyo submitted that together, the information on the opening page and page 16 provided clear guidance to patients to read all information provided in the document and PIL. It was clear what actions they should take should they experience a side effect from their Lixiana prescription, with an explanation of how these types of side effects (bleeding) could occur with this type of medication (anticoagulant) for added context. By inclusion of the description 'if you experience ANY side effects' the material made clear that ALL side effects should be reported, even if they were not directly listed.

The information contained in this booklet was provided as a support for patients, in a language and tone that was tailored to the audience and was designed to complement the patient information leaflet rather than be a verbatim copy. Therefore, Daiichi Sankyo denied that there had been a breach of Clauses 6.1, 6.2 and 6.4, and by extension Clauses 5.1 and 2.

Venous thromboembolism booklet

Daiichi Sankyo submitted that there was no requirement in the Code that information provided to patients in a PIL must be provided verbatim in company-produced material intended for patient support. Nevertheless, in the document in question (EDX/20/1071) the opening page stated in bold typeface '**It's important to read the Lixiana package leaflet provided with your medicine'** underneath the adverse event reporting statement. Moreover, this was bookended on page 16 with the additional statement, again in bold typeface:

> '**Bleeding is not always obvious. If you experience any side effects, talk to your doctor or pharmacist. It is important not to stop taking Lixiana without talking to them first'.**

Daiichi Sankyo submitted that together, the information on the opening page and page 16 provided clear guidance to patients to read all information provided in the document and PIL. It was clear what actions they should take should they experience a side effect from their Lixiana prescription, with an explanation of how these types of side effects (bleeding) could occur with this type of medication (anticoagulant) for added context. By inclusion of the description 'if you experience ANY side effects' the material made clear that ALL side effects should be reported, even if they were not directly listed.

Daiichi Sankyo submitted that the information contained in this booklet was provided as a support for patients, in a language and tone that was tailored to the audience and was designed to complement the patient information leaflet rather than be a verbatim copy. Therefore, Daiichi

Sankyo denied that there had been a breach of Clauses 6.1, 6.2 and 6.4, and by extension there was no evidence of a breach of Clauses 5.1 and 2.

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.

PANEL RULING

The Panel considered that it was a legitimate activity for a company to produce material for patient support which was intended to be provided to patients once they had been prescribed a particular medicine.

In the Panel's view, such patient support material must not be inconsistent with the package leaflet/patient information leaflet (PIL) and must comply with all the requirements of the Code including that it must not mislead the patient as to the safety profile of the medicine as stated in the PIL.

Whilst the Panel accepted that there was no explicit requirement in the Code for all information in the PIL to be reproduced in each piece of company produced patient support material, the Panel considered that much would depend on the purpose of the material and its content and layout. If the purpose of such company material was not to reproduce all the important information for patients as stated in the PIL, then it would be prudent that the material did not misleadingly imply that it did.

Atrial fibrillation

The Panel noted that the booklet titled 'Understanding your treatment for atrial fibrillation' stated on the front page that it was for patients prescribed Lixiana (edoxaban) and included a prominent reporting of side effects statement. The front page also stated, in bold typeface, 'It's important to read the Lixiana package leaflet provided with your medicine.'

Page 4 of the material stated that if the patient would like more information, he/she could refer to the leaflet that comes in the pack or visit Daiichi Sankyo's website for patients prescribed Lixiana. It further stated 'This booklet has been developed to provide useful information, but is not intended to replace your doctor's advice. If you have any concerns or questions about your health or medication, your doctor is always the best person to ask.' This page also then repeated the reporting of side effects statement.

The Panel noted that the 20 page booklet contained much broader information than the patient information leaflet (PIL). It explained, amongst other things, with the addition of simple pictures, what atrial fibrillation was, how many people it affected in the UK, how a blood clot could cause a stroke and what lifestyle changes could help reduce the risk of stroke. It also included information about how Lixiana worked, how it should be taken, potential side effects, other considerations when taking Lixiana and details of other sources of information including details of patient organisations.

Page 16 of the booklet was headed 'What about potential side effects?' and stated:

'Like all medication, Lixiana can cause side effects, although not everybody experiences them.

Like other anticoagulant medication, Lixiana is designed to thin your blood and help prevent blood clots. So you may have an increased risk of bleeding while taking it.

Speak to your doctor immediately if you experience any of the following signs of bleeding:

• Bruising or bleeding under the skin
• Nose bleed or cuts that take a long time to stop bleeding
• Red or dark brown urine
• Coughing up or vomiting blood or ground coffee-like material
• Red or black stools
• Bleeding gums
• Bleeding that does not stop by itself
• Abnormally heavy periods or unexpected vaginal bleeding

Bleeding is not always obvious. If you experience any side effects, talk to your doctor or pharmacist. It is important not to stop taking Lixiana without talking to them first.

Please refer to package leaflet for further information about adverse effects.'

The Panel noted that the next three pages of the booklet were headed 'Is there anything else you should consider when taking Lixiana?' and referred to, amongst other things, the patient alert card, visiting the dentist, what to do if injured and what to do if you think you might be pregnant or are planning pregnancy.

The Panel noted there was additional information in Section 4 of the PIL, which was not listed in the booklet, including in relation to bleeding, such as the signs of excessive bleeding (exceptional weakness, tiredness, paleness, dizziness, headache or unexplained swelling) which the PIL stated that the patient should consult their doctor immediately about if experienced.

The Panel considered the immediate and overall impression of the booklet to a patient. The Panel considered, on the balance of probabilities, that the page 'what about potential side effects' misleadingly implied that the list given was a complete list of all potential side effects which was not so. In particular, there was the omission of additional information from section 4 of the PIL in relation to signs of excessive bleeding, which the PIL stated that the patient should consult their doctor immediately about; in the Panel's view, this would be important information for a patient booklet which specifically referred to when a patient should contact their doctor. The following pages headed 'Is there anything else you should consider when taking Lixiana?' compounded the misleading impression given that this booklet contained all the important information a patient needed before/during treatment with Lixiana which was not so.

In the Panel's view, the statement 'Please refer to package leaflet for further information about adverse effects' on the potential side effects page in question did not negate the misleading impression given that the booklet contained all the relevant safety information that the patient needed to consider when taking Lixiana, particularly in relation to bleeding, which was not so. In the Panel's view, exceptional weakness, tiredness, paleness, dizziness, headache or

unexplained swelling might not be readily recognised as signs of excessive bleeding by the patient and therefore the omission of such information, in a section of the booklet which was instructing patients when to speak to their doctor about bleeding, was misleading and might prejudice patient safety. The Panel considered that company produced material for patients had to be capable of standing alone with regard to the requirements of the Code and could not rely on qualification in the patient information leaflet. **A breach of Clause 6.1** was therefore ruled in this regard. The Panel considered the misleading impression given that the booklet contained all the relevant information that the patient needed in relation to bleeding was incapable of substantiation and **a breach of Clause 6.2** was ruled.

The Panel, noting there was nonetheless safety information in relation to bleeding, did not consider that the booklet implied that the medicine had no side effects or no bleeding risk and **no breach of Clause 6.4** was ruled.

The Panel noted Daiichi Sankyo's submission that the booklet was designed to complement the patient information leaflet rather than be a verbatim copy of it. However, in the Panel's view, this was not made clear in the material. Whilst the Panel accepted that the front page of the booklet stated 'It's important to read the Lixiana Package leaflet provided with your medicine', the Panel considered that it might not be clear to all patients that the 20 page booklet produced by Daiichi Sankyo was not a substitute for the package leaflet or that the package leaflet contained additional important information on the use of the medicine that was not in the booklet. The Panel considered that Daiichi Sankyo had failed to maintain high standards in this regard and a **breach of Clause 5.1** was ruled.

Clause 2 was a sign of particular censure and was reserved for such use. Prejudicing patient safety was an example of an activity likely to lead to a breach of this clause. Companies needed to take the utmost care when producing materials for patients to ensure that patients could not be misled as to the safety profile of the medicine. The Panel considered that the misleading impression given by the booklet, which implied that it contained all of the important safety information that the patient needed to consider before and during Lixiana treatment, particularly in relation to bleeding, which was not so, meant that Daiichi Sankyo had reduced confidence in and brought discredit upon the industry and **a breach of Clause 2** was ruled.

Venous thromboembolism

The Panel noted that the booklet titled 'Understanding your treatment for venous thromboembolism' stated on the front page that it was for patients prescribed Lixiana (edoxaban) and included a prominent reporting of side effects statement. The front page also stated, in bold typeface, 'It's important to read the Lixiana package leaflet provided with your medicine.'

Page 4 of the material stated that if the patient would like more information, he/she could refer to the leaflet that comes in the pack or visit Daiichi Sankyo's website for patients prescribed Lixiana. It further stated 'This booklet has been developed to provide useful information, but is not intended to replace your doctor's advice. If you have any concerns or questions about your health or medication, your doctor is always the best person to ask.' This page also repeated the side effect reporting statement.

The Panel noted that the 20 page booklet contained much broader information than the patient information leaflet (PIL). It explained, amongst other things, with the addition of simple pictures,

what venous thromboembolism was, its prevalence, symptoms and what lifestyle changes that could reduce risk of venous thromboembolism. It also included information about how Lixiana worked, how it should be taken, potential side effects, other considerations when taking Lixiana and details of other sources of information including details of patient organisations.

Page 16 of the booklet was headed 'What about potential side effects?' and stated:

> **'Like all medication, Lixiana can cause side effects, although not everybody experiences them.**
>
> Like other anticoagulant medication, Lixiana is designed to thin your blood and help prevent blood clots. So you may have an increased risk of bleeding while taking it.
>
> **Speak to your doctor immediately if you experience any of the following signs of bleeding:**
>
> • Bruising or bleeding under the skin
> • Nose bleed or cuts that take a long time to stop bleeding
> • Red or dark brown urine
> • Coughing up or vomiting blood or ground coffee-like material
> • Red or black stools
> • Bleeding gums
> • Bleeding that does not stop by itself
> • Abnormally heavy periods or unexpected vaginal bleeding
>
> **Bleeding is not always obvious. If you experience any side effects, talk to your doctor or pharmacist. It is important not to stop taking Lixiana without talking to them first.'**

The Panel noted that, unlike the Atrial Fibrillation booklet ruled upon above, the Venous Thromboembolism booklet did not refer the patient to see the package leaflet for further information about adverse effects on the 'What about potential side effects?' page.

The Panel noted that the next three pages of the booklet were headed 'Is there anything else you should consider when taking Lixiana?' and referred to, amongst other things, the patient alert card, visiting the dentist, what to do if injured and what to do if you think you might be pregnant or are planning pregnancy.

The Panel noted there was additional information in Section 4 of the PIL, which was not listed in the booklet, including in relation to bleeding, such as the signs of excessive bleeding (exceptional weakness, tiredness, paleness, dizziness, headache or unexplained swelling) which the PIL stated that the patient should consult their doctor immediately about if experienced.

The Panel considered the immediate and overall impression of the booklet to a patient. The Panel considered, on the balance of probabilities, that the page 'what about potential side effects' misleadingly implied that the list given was a complete list of all potential side effects which was not so. In particular, there was the omission of additional information from section 4 of the PIL in relation to signs of excessive bleeding, which the PIL stated that the patient should consult their doctor immediately about; in the Panel's view, this would be important information

for a patient booklet which specifically referred to when a patient should contact their doctor. The following pages headed 'Is there anything else you should consider when taking Lixiana?' compounded the misleading impression given that this booklet contained all the important information a patient needed before/during treatment with Lixiana which was not so.

In the Panel's view, exceptional weakness, tiredness, paleness, dizziness, headache or unexplained swelling might not be readily recognised as signs of excessive bleeding by the patient and therefore the omission of such information, in a section of the booklet which was instructing patients when to speak to their doctor about bleeding, was misleading and might prejudice patient safety. The Panel considered that company produced material for patients had to be capable of standing alone with regard to the requirements of the Code and could not rely on qualification in the patient information leaflet. **A breach of Clause 6.1** was therefore ruled in this regard. The Panel considered the misleading impression given that the booklet contained all the relevant information that the patient needed in relation to bleeding was incapable of substantiation and **a breach of Clause 6.2** was ruled.

The Panel, noting there was nonetheless safety information in relation to bleeding, did not consider that the booklet implied that the medicine had no side effects or no bleeding risk and **no breach of Clause 6.4** was ruled.

The Panel noted Daiichi Sankyo's submission that the booklet was designed to complement the patient information leaflet rather than be a verbatim copy of it. However, in the Panel's view, this was not made clear in the material. Whilst the Panel accepted that the front page of the booklet stated 'It's important to read the Lixiana Package leaflet provided with your medicine', the Panel considered that it might not be clear to all patients that the 20 page booklet produced by Daiichi Sankyo was not a substitute for the package leaflet or that the package leaflet contained additional important information on the use of the medicine that was not in the booklet. The Panel considered that Daiichi Sankyo had failed to maintain high standards in this regard and a **breach of Clause 5.1** was ruled.

Clause 2 was a sign of particular censure and was reserved for such use. Prejudicing patient safety was an example of an activity likely to lead to a breach of this clause. Companies needed to take the utmost care when producing materials for patients to ensure that patients could not be misled as to the safety profile of the medicine. The Panel considered that the misleading impression given by the booklet, which implied that it contained all of the important safety information that the patient needed to consider before and during Lixiana treatment, particularly in relation to bleeding, which was not so, meant that Daiichi Sankyo had reduced confidence in and brought discredit upon the industry and **a breach of Clause 2** was ruled.

Complaint received 1 April 2022

Case completed 14 April 2023