CASE AUTH/2822/2/16

BAYER v DAIICHI-SANKYO

Promotion of Lixiana

Bayer Healthcare complained about a Lixiana (edoxaban) leavepiece produced by Daiichi-Sankyo UK.

The detailed response from Daiichi Sankyo is given below.

Bayer alleged that the imagery of a crossed-out blood test machine with the claim 'No regular anticoagulation level monitoring required' was misleading, not capable of substantiation and was inconsistent with the SPC as the Lixiana SPC listed several circumstances in which regular monitoring of anticoagulation levels might be needed. It suggested there was no need for any blood-testing at all whereas in contrast to some other NOACs, patients on Lixiana were required to undergo renal and liver function tests. Bayer alleged that it put patient safety at risk by undermining rational use of the medicine. Bayer further alleged that the image itself was in breach of the Code and the associated claim was inconsistent with the SPC. High standards had not been maintained.

The Panel noted that the leavepiece, headed 'Simple and convenient for patients and prescribers' followed by 'New Once-Daily Lixiana Another Step Ahead', referred to the indication on page 1, gave efficacy information on page 2 and set out the dosing regimens on page 3. The statement 'Liver function testing and renal function (CrCl) assessment should be carried out prior to initiating Lixiana and afterwards when clinically indicated ….' appeared on page 3 and referred readers to the SPC for more guidance.

With regard to the graphic, the Panel noted that beneath the illustration the claim referred to anticoagulation monitoring rather than blood monitoring. It noted Daiichi-Sankyo's submission that the graphic resembled the devices recommended by NICE for anticoagulation and no such hand held device existed for renal/liver function testing. In the Panel's view the graphic with the line through it would not be read as implying no blood testing at all was required as alleged. The claim immediately beneath referred to anticoagulation. In the Panel's view the graphic in its context was not misleading, nor did it fail to promote rational use of the medicine and no breaches of the Code were ruled. The Panel did not agree that the graphic was inconsistent with the SPC or that Daiichi-Sankyo had failed to maintain high standards and no breaches of the Code were ruled.

Bayer further alleged that the claim 'No scheduled high-to-low dose transition at initiation in VTE [venous thromboembolism] patients' beneath a graphic of what appeared to be a calendar was misleading, not capable of substantiation and was inconsistent with the SPC because it disregarded the requirement for high-dose parenteral anticoagulation for the first 5 days after initiation of venous thromboembolism (VTE) treatment, before Lixiana therapy could start. Bayer alleged that it encouraged the irrational use of Lixiana and thus Daiichi Sankyo had failed to maintain high standards.

The Panel noted that Lixiana required at least 5 days' treatment with parenteral anticoagulant before it could be used for treatment of DVT, PE or prevention of recurrent VTE. Bayer's product Xarelto did not need pre-treatment with another product. Its dosing regimen changed from 15mg twice daily (Day 1-21) to 20mg once-daily from Day 22 onwards. The Panel noted that page 2 of the leavepiece in relation to DVT or PE patients referred to 'following initial use of heparin for at least 5 days' and page 3 stated 'VTE patients should receive heparin for at least 5 days before initiating Lixiana'. Page 4 was headed 'once-daily Lixiana' and the claim at issue was preceded by a claim 'Consistent Lixiana dosing regimen across both NVAF and VTE indications'.

The Panel considered that the claim 'No scheduled high to low dose transition in initiation in VTE patients' was an accurate description of the dosing regimen for Lixiana once the patient had started treatment with that product. There was no mention on page 4 of the need for pre-treatment with heparin when prescribing for VTE patients. Whilst there was mention of such use on pages 2 and 3, the page and claim in question had to be capable of standing alone with regard to compliance with the Code. The Panel did not consider that the claim was sufficiently clear that VTE patients could only be given once-daily Lixiana after at least 5 days of treatment with heparin. The phrase 'initiation in VTE patients' could be read in two ways: the whole treatment for VTE or that part of the treatment of VTE when Lixiana was initiated. It was not clear. In the Panel's view the page implied that the use of Lixiana in patients with NVAF and VTE were similar and further that the only difference in treating VTE patients with Lixiana or other NOACs was that Lixiana was the only once-daily treatment at the same dose for the whole treatment period. The claim was misleading and a breach of the Code was ruled. The Panel considered that the misleading implication was not capable of substantiation and thus ruled a breach of the Code. The claim did not promote rational use of Lixiana, it was inconsistent with the SPC and the Panel ruled breaches of the Code. The Panel also ruled a breach of the Code as high standards had not been maintained.

Bayer noted the claim 'Superior reduction in major bleeding vs well-controlled warfarin' [NVAF population] and alleged that there was no evidence that the major-bleeding reduction vs warfarin

conferred by Lixiana was in any way 'superior' to the reduction vs warfarin that was conferred by any other NOAC. Use of the phrase 'superior reduction' rather than the more conventional 'significant reduction' was ambiguous and appeared to be a deliberate choice that implied that the reduction in bleeding versus warfarin seen with Lixiana was greater than the significant reduction in major bleeding observed in other trials with NOACs in the atrial fibrillation indication which was misleading, not capable of substantiation; implied that Lixiana had some special merit which could not be substantiated and was disparaging of Bayer's product Xarelto. 'Superior' was also alleged to be a hanging comparison.

Bayer alleged that similarly, the claim 'Superior reduction in clinically relevant bleeding vs well-controlled warfarin' [VTE population] was misleading and disparaging; it was not clear what 'superior' was compared to. 'Reduction' was versus warfarin but 'superior reduction' indicated that the reduction was greater than some other reduction, implying a head-to-head comparison where one did not exist.

The Panel did not consider that the description in the leavepiece 'Superior reduction' would necessarily be read in the statistical sense as submitted by Daiichi-Sankyo. No p number was given. The layout and context could imply that superior reduction in major bleeding was broader than a comparison between Lixiana and warfarin. This was due to the use of upper case for the claim 'SUPERIOR REDUCTION IN MAJOR BLEEDING' and that the claim was highlighted in green. The Panel accepted that the claim was qualified by 'Vs. well-controlled warfarin'. This appeared in smaller black type beneath and was not highlighted in green but was, nonetheless, sufficiently prominent to qualify the claim in question. The Panel considered that, on balance, the claim was not misleading or ambiguous as alleged as it did not claim that the difference between Lixiana and warfarin was superior to that seen with other NOACs. There was no mention of other NOACs on the page. The comparisons were all with warfarin. The Panel therefore ruled no breaches of the Code. The Panel did not consider that the claim disparaged Xarelto or was a hanging comparison. No breaches of the Code were ruled.

The Panel noted its ruling above and considered that the position was similar in relation to the VTE claims. The Panel therefore ruled no breaches of the Code.

Bayer further alleged that the claims 'Once-daily Lixiana is simple and convenient' and 'Once-daily Lixiana is simple and convenient for patients and prescribers' underplayed the inherent complexity and inconvenience of needing 5 days of injected low molecular weight heparin (LMWH) prior to being able to start Lixiana in the VTE population. Bayer alleged that the above claims were misleading, incapable of substantiation and 'simple' was contrary to the SPC.

The Panel agreed with both companies that Lixiana like other similar medicines was not necessarily simple to use. It noted Daiichi-Sankyo's submission that it was the once-daily dose which meant that Lixiana was simple to use. Page 3 set out the dosing regimen 60mg once-daily (or 30mg once-daily when a reduced dose was needed) for eligible NVAF and VTE patients. This page also referred to the need for pre-treatment for VTE patients with heparin. Page 5 set out the dosing regimens for Lixiana, rivaroxaban, dabigatran and apixaban.

The Panel noted that treatment of eligible NVAF patients with Xarelto was also once-daily and the other two products dabigatran and apixaban were dosed twice daily in this indication.

In VTE Lixiana was once-daily (following heparin pre-treatment) whereas whilst there was no heparin pre-treatment with Xarelto or apixaban there was a dose transition from 15mg twice-daily for 3 weeks to 20mg once-daily for Xarelto and from 10mg twice-daily for 7 days to 5mg twice-daily for apixaban. Dabigatran was 150mg twice-daily after requiring heparin for at least 5 days.

The Panel considered that it was not unreasonable to claim that Lixiana's once-daily dosing regimen was simple and convenient including in VTE once treatment with Lixiana had commenced. The requirement to receive heparin for at least five days before initiating Lixiana in VTE patients was stated on pages 3 and 5. The Panel was concerned that on page 5 the requirement to receive heparin was only visible when, and if, the reader pulled a tab to reveal the VTE dosing regimens. However, on balance, the Panel did not consider that the claims as used on pages 3 and 5 were misleading as alleged, it was sufficiently clear that simple and convenient referred to once-daily dosing. The Panel ruled no breach of the Code. As such the claims at issue were capable of substantiation and therefore no breach of the Code was ruled. Lixiana was used for VTE patients once-daily after treatment with that product had commenced, ie after at least 5 days' treatment with heparin. The term 'simple' within the context of the claims in question and rulings of no breach of the Code above was not inconsistent with the SPC. The Panel thus ruled no breach of the Code.

Lastly Bayer alleged that a graph which compared Lixiana with rivaroxaban, dabigatran and apixaban in relation to dose and number of tablets for NVAF and VTE based on 30 days of treatment with a timescale from 0 to 6 months and the associated numerical claims for VTE were misleading, unsafe and defamatory to its product Xarelto. Calling the point of transition from LMWH to Lixiana 'time zero' was alleged to be misleading, unsafe and incompatible with the SPC. Time zero should be from the time of diagnosis/initiation of anticoagulation. Starting from the point of switch to Lixiana implied that the first 5 days of anticoagulation were not needed. This was essentially a 'suppressed zero' of the time axis, which specifically breached the Code. The omission of the first 5 days of injections furthermore downplayed the complexity, inconvenience and discomfort of using Lixiana relative to Xarelto which was pictured alongside and the comparison was alleged to be misleading and disparaging of Xarelto. Bayer had a further concern over the

choice of a 30-days' treatment horizon for the commercial comparison. The Lixiana SPC defined even 'short term treatment' as at least three months' duration. The choice of a 30-day treatment horizon was thus alleged to fail to promote rational prescribing in a manner contradictory to the SPC. In summary, the choice of 30 days was alleged to be inaccurate; misleading by comparison; visually misrepresentative; failed to promote rational use of any of the products; contrary to the SPC and was defamatory of Xarelto. Bayer alleged that overall this constituted a further failure to maintain high standards.

The Panel considered that the page was clear that time zero was the time of initiation of treatment with Lixiana and not when VTE was diagnosed and treatment commenced. The Panel did not accept that the first 5 days of injections had been omitted as alleged, the graph clearly referred to the need for treatment with heparin for Lixiana for VTE and thus it ruled no breaches of the Code in relation to Bayer's allegation that this omission downplayed the complexity, inconvenience and discomfort of using Lixiana compared to Xarelto. In that regard, Xarelto was not disparaged and no breach of the Code was ruled. The heading to the graph referred to the first 30 days of treatment with NOACs. The graph did not imply that pre-treatment with heparin was not necessary as alleged. The Panel ruled no breaches of the Code on this point. Nor did the Panel consider that there was a suppressed zero of the time axis as alleged; it was clear that the axis related to the start of treatment with a NOAC. No breach of the Code was ruled.

The Panel considered that it was misleading and unfair to compare dosing transition and pill burden for 30 days where Lixiana was indicated for at least 3 months ie 90 days. It was true that Lixiana had an advantage regarding the number of pills to be taken at either 30 days or 90 days but the difference at 90 days was less than at 30 days. When treating VTE there was an additional burden in that heparin for at least 5 days was also required to treat VTE. It was more complex to treat with heparin than with a tablet.

The Panel noted its comments about the 30 day treatment period above. The Panel considered the graph was misleading in relation to the 30 days and ruled a breach of the Code. The graph did not give a fair and balanced view of the pill burden and was ruled in breach of the Code. On balance, the Panel did not consider that the graph failed to promote rational prescribing as alleged and no breach of the Code was ruled.

The Panel considered that the 30-day treatment emphasis meant that rational prescribing had not been promoted as the leavepiece did not refer to the treatment with Lixiana as at least 3 months as set out in the SPC. The Panel ruled a breach of the Code as alleged. In this regard, the graph was inconsistent with the SPC and a breach of the Code was ruled.

The Panel noted its rulings above and considered that in relation to the graph Daiichi-Sankyo had not maintained high standards and a breach of the Code was ruled.

Bayer Healthcare submitted a complaint about the promotion of Lixiana (edoxaban) by Daiichi-Sankyo UK Limited.

The material at issue (ref EDX/15/0090 June 2015) was a six-page gate-folded leavepiece used at the European Society of Cardiology meeting in London and which was for use by the sales team with health professionals either face-to-face or at meetings.

Lixiana was a novel oral anticoagulant (NOAC) for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation (NVAF) with one or more risk factors such as congestive heart failure (CHF), hypertension, over 75 years old, diabetes mellitus, prior stroke or transient ischaemic attack (TIA). It was also indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults.

The leavepiece was headed 'Simple and convenient for patients and prescribers' followed by 'New Once-Daily Lixiana (edoxaban) Another Step Ahead'. The indications were given beneath the heading.

Bayer marketed Xarelto (rivaroxaban) which was also a NOAC.

1 Crossed-out image of a blood-test machine with the claim 'No regular anticoagulation level monitoring required'

The claim appeared on page 4 which was headed 'Once-Daily Lixiana'. Five features of the product were illustrated with details of the feature below the illustration. The final graphic was of what appeared to be a hand held machine reading 2.8 with a line through it with the claim 'No regular anticoagulation level monitoring required' (referenced to the Lixiana summary of product characteristics (SPC)) beneath the graphic.

COMPLAINT

Bayer alleged that the use of the imagery of a crossed-out blood test machine was inappropriate for several reasons. Firstly, the Lixiana SPC listed several circumstances in which regular monitoring of anticoagulation levels might be needed. For instance, switching to or from a vitamin K antagonist (VKA); overdose; emergency surgery. The claim was alleged to be misleading in breach of Clause 7.2, not capable of substantiation in breach of Clause 7.4 and incompatible with the SPC in breach of Clause 3.2.

The prominent image of a crossed-out blood monitor was of particular concern as it suggested there was no need for any blood-testing at all – a *de facto* claim which was furthermore not qualified in any way by the text underneath which dealt only with anticoagulation monitoring. In contrast to some other NOACs, patients on Lixiana were required to undergo renal and liver function tests prior to initiation and periodically during treatment, as stated in Sections 4.2 and 4.4 of the Lixiana SPC.

Use of the graphic of a crossed-out blood monitor without mentioning the need for initial and regular liver and renal testing was alleged to be misleading in breach of Clause 7.2 in a way that put patient safety at risk through undermining rational use of the medicine in breach of Clause 7.10. The associated artwork was alleged to be in breach of Clause 7.8 and the *de facto* claim contrary to the label in breach of Clause 3.2. Furthermore, this cherry-picking of blood test information was an example of Daiichi-Sankyo putting commercially-favourable (but misleading) claims ahead of patient safety. Bayer alleged a failure to maintain high standards in breach of Clause 9.1.

RESPONSE

Daiichi-Sankyo submitted that the imagery was appropriate in the context of the leavepiece. The graphic appeared on the fourth or fifth page of the leavepiece, on a summary page of the key features of edoxaban. It was not used in isolation in any other materials and should therefore be considered in the context of the leavepiece.

The graphic depicted a self-monitoring coagulometer international normalised ratio (INR) testing device, evidenced by the number '2.8' on the readout. Daiichi-Sankyo submitted that this type of device was becoming more and more common and had even been recommended by the National Institute for Health and Care Excellence (NICE).

The graphic very closely reassembled the devices that were in use and was not meant to mislead health professionals into believing that it represented a general blood test device. In addition, Daiichi-Sankyo UK submitted it had been very explicit with the wording 'No routine anticoagulation level monitoring required', as per the Lixiana SPC. The need to ascertain renal function and liver function prior to initiation of Lixiana was clearly stated on page 3 of the leavepiece. This 'dosing' page was discussed and agreed with the Medicines and Healthcare products Regulatory Agency (MHRA) as part of prevetting of materials. Finally, Daiichi-Sankyo UK had repeatedly pointed out to Bayer that the need to ascertain liver and renal function was common to all NOACs. Daiichi-Sankyo refuted breaches of Clauses 7.2, 7.4, 9.1 and 3.2.

In response to a request for further information, Daiichi-Sankyo submitted that the graphic representative of the device was meant to represent INR monitoring, a practice familiar to health professionals who managed patients on warfarin. While it was usually performed in a central laboratory, NICE (DG 14 2014) had issued recent guidance about the use of self-monitoring of INR by patients, two devices specifically, the Roche Coagucheck XS system and the InRatio 2 PT/INR. Daiichi-Sankyo submitted that the graphic closely resembled the devices that were recommended by NICE for use and there was no intention to claim that no other blood tests were required. The caption below the graphic clearly stated the reference to anticoagulation monitoring only.

No such handheld device existed for renal/liver function testing to Daiichi-Sankyo's knowledge and indeed there would not be a clinically relevant reason for a patient to self-test for those parameters. Monitoring of renal and liver function were part of the routine management of patients on anticoagulation (NICE CG 180) and would be performed on a regular basis by the physician via a central laboratory as part of the usual blood test panel via an automated instrument. An image of such a machine was provided which Daiichi-Sankyo submitted was unlikely to be confused with its graphic.

PANEL RULING

The Panel noted that the leavepiece referred to the indication on page 1, gave efficacy information on page 2 and set out the dosing regimens on page 3. The statement 'Liver function testing and renal function (CrCl) assessment should be carried out prior to initiating Lixiana and afterwards when clinically indicated ….' appeared on page 3 and referred readers to the SPC for more guidance.

With regard to the graphic, the Panel noted that beneath the illustration the claim referred to anticoagulation monitoring rather than blood monitoring. It noted Daiichi-Sankyo's submission that the graphic resembled the devices recommended by NICE for anticoagulation and no such hand held device existed for renal/liver function testing. In the Panel's view the graphic with the line through it would not be read as implying no blood testing at all was required as alleged. The claim immediately beneath referred to anticoagulation. In the Panel's view the graphic in its context was not misleading, nor did it fail to promote rational use of the medicine. No breach of Clauses 7.2 and 7.10 was ruled and thus no breach of Clause 7.8 was also ruled.

The Panel did not agree that the graphic was inconsistent with the SPC and thus ruled no breach of Clause 3.2. Daiichi-Sankyo had not failed to maintain high standards as alleged and the Panel ruled no breach of Clause 9.1.

2 Claim 'No scheduled high-to-low dose transition at initiation in VTE [venous thromboembolism] patients'

The claim appeared on page 4 beneath a graphic of what appeared to be a calendar.

COMPLAINT

Bayer alleged that this claim was deceptive and contrary to the label, because it disregarded the requirement for high-dose parenteral anticoagulation for the first 5 days after initiation of venous thromboembolism (VTE) treatment, before Lixiana therapy could start. In fact, what was required after initiation in VTE patients was far more than just a change in dose – a whole change of medicine class and mode as well as route of delivery was necessary. Bayer alleged that this claim was misleading in breach of Clause 7.2; not capable of substantiation

in breach of Clause 7.4 and contrary to the SPC, in breach of Clause 3.2 in a way that encouraged wrong and unsafe use of Lixiana in breach of Clause 7.10. Bayer alleged that the clear failure to maintain high standards was in breach of Clause 9.1.

RESPONSE

Daiichi-Sankyo UK stated that the claim accurately reflected the posology of Lixiana for patients being treated for a VTE event ie at initiation with Lixiana, the selected dose did not need to be routinely altered. This was in contrast to eg rivaroxaban which required 21 days of an initial regimen of twice a day 15mg tablets followed by once a day 20mg (or 15mg depending on risk of bleeding) or apixaban (Eliquis, Bristol Myers Squibb product) which required an initial week course of two 5mg tablets twice a day, followed by one 5mg tablet twice a day for 6 months then one 2.5mg tablet twice a day.

Lixiana was the third factor Xa inhibitor to market and Daiichi-Sankyo wanted to ensure that this need for dose transition at initiation was not applied to patients on Lixiana as this would result in patients being under dosed and potentially put at risk of recurrent events. Daiichi-Sankyo denied that the need for a heparin lead-in was hidden. The need for a heparin lead-in was mentioned in four instances in the leavepiece. Daiichi-Sankyo refuted breaches of Clauses 3.2, 7.2, 7.4, 7.10 and 9.1.

PANEL RULING

The Panel noted that Lixiana required at least 5 days' treatment with parenteral anticoagulant before it could be used for treatment of DVT, PE or prevention of recurrent VTE.

Bayer's product Xarelto did not need pre-treatment with another product. Its dosing regimen changed from 15mg twice daily (Day 1-21) to 20mg once-daily from Day 22 onwards.

The Panel noted that page 2 of the leavepiece in relation to DVT or PE patients referred to 'following initial use of heparin for at least 5 days' and page 3 stated 'VTE patients should receive heparin for at least 5 days before initiating Lixiana'.

Page 4 was headed 'once-daily Lixiana' and the claim at issue was preceded by a claim 'Consistent Lixiana dosing regimen across both NVAF and VTE indications'.

The Panel considered that the claim 'No scheduled high to low dose transition in initiation in VTE patients' was an accurate description of the dosing regimen for Lixiana once the patient had started treatment with that product. There was no mention on page 4 of the need for pre-treatment with heparin when prescribing for VTE patients. Whilst there was mention of such use on pages 2 and 3, the page and claim in question had to be capable of standing alone with regard to compliance with the Code. The Panel did not consider that the claim was sufficiently clear that VTE patients could only be given once-daily Lixiana after at least 5 days of treatment with heparin. The phrase 'initiation in VTE patients' could be read in two ways: the whole treatment for VTE or that part of the treatment of VTE when Lixiana was initiated. It was not clear. In the Panel's view the page implied that the use of Lixiana in patients with NVAF and VTE were similar and further that the only difference in treating VTE patients with Lixiana or other NOACs was that Lixiana was the only once-daily treatment at the same dose for the whole treatment period. The claim was misleading and a breach of Clause 7.2 was ruled. The Panel considered that the misleading implication was not capable of substantiation and thus ruled a breach of Clause 7.4. The claim did not promote rational use of Lixiana and a breach of Clause 7.10 was ruled. It was inconsistent with the SPC and thus a breach of Clause 3.2 was ruled. Given its rulings above the Panel also ruled a breach of Clause 9.1 as high standards had not been maintained.

3 Claim 'Superior reduction in major bleeding vs well-controlled warfarin' [NVAF population]

The claim appeared on the left-hand side of page 2 beneath the heading 'For your patients with NVAF:' which was followed by 'Proven Efficacy' and 'Comparable to well-controlled warfarin in the prevention of stroke/SEE' [systemic embolic events]. Then followed the claim at issue 'Superior reduction in major bleeding' and 'Vs. well-controlled warfarin'. The page was designed such that 'Proven Efficacy' and 'Superior Reduction in major bleeding' were in upper case and highlighted in green. These claims were followed by 'Comparable to well-controlled warfarin in the prevention of stoke/SEE' and 'Vs. well-controlled warfarin' in smaller black type (with no highlighting) beneath each respectively.

COMPLAINT

Bayer stated that this claim used in the leavepiece also appeared on the promotional stand. The company alleged there was no evidence that the major-bleeding reduction vs warfarin conferred by Lixiana was in any way 'superior' to the reduction vs warfarin that was conferred by any other NOAC. The use of the phrase 'superior reduction' rather than the more conventional 'significant reduction' was ambiguous and appeared to be a deliberate choice that implied that the reduction in bleeding versus warfarin seen with Lixiana was greater than the significant reduction in major bleeding observed in other trials with NOACs in the atrial fibrillation indication. Bayer alleged that this claim was therefore misleading in breach of Clause 7.2, not capable of substantiation in breach of Clause 7.4; implied that Lixiana had some special merit which could not be substantiated in breach of Clause 7.10 and was disparaging of Bayer's product Xarelto in breach of Clause 8.1. 'Superior' was also alleged to be technically a hanging comparison in breach of Clause 7.2.

RESPONSE

Daiichi-Sankyo stated that the claims in points 4 and 5 (below) were very specific to the comparison of

Lixiana to warfarin and used the term 'superior' in its statistical sense. The claims referred to the primary safety endpoint of the registration trials of Lixiana and in both, Lixiana was superior to well-controlled warfarin at reducing the primary safety endpoint, with a very high degree of statistical significance (p=0.0009 for ENGAGE-AF trial and p=0.004 for HOKUS AI trial). No comparison to other NOACs was implied or intended.

At the face-to-face meeting, Bayer agreed that the claim 'Superior to well-controlled warfarin at reducing major/clinically relevant bleeding' would be acceptable. However, Daiichi-Sankyo decided against changing the claim as this would imply that the original claim was misleading. Daiichi-Sankyo stood by the original phrase. Daiichi-Sankyo refuted breaches of Clauses 7.2, 7.4, 7.10 and 8.1.

PANEL RULING

The Panel did not consider that the description 'Superior reduction' would necessarily be read in the statistical sense as submitted by Daiichi-Sankyo. No p number was given. The layout and context could imply that superior reduction in major bleeding was broader than a comparison between Lixiana and warfarin. This was due to the use of upper case for the claim 'SUPERIOR REDUCTION IN MAJOR BLEEDING' and that the claim was highlighted in green. The Panel accepted that the claim was qualified by 'Vs. well-controlled warfarin'. This appeared in smaller black type beneath and was not highlighted in green but was, nonetheless, sufficiently prominent to qualify the claim in question. The Panel considered that, on balance, the claim was not misleading or ambiguous as alleged as it did not claim that the difference between Lixiana and warfarin was superior to that seen with other NOACs. There was no mention of other NOACs on page 2. The comparisons were all with warfarin. The Panel therefore ruled no breach of Clauses 7.2 and 7.4. The Panel also ruled no breach of Clause 7.10. The Panel did not consider the claim disparaged Xarelto as alleged and no breach of Clause 8.1 was ruled. Nor did the Panel consider the claim was a hanging comparison. No breach of Clause 7.2 was ruled in this regard.

4 Claim 'Superior reduction in clinically relevant bleeding vs well-controlled warfarin' [VTE population]

The claim appeared on the right-hand side of page 2 beneath the heading 'For your patients with DVT or PE, following initial use of heparin for at least 5 days:' which was followed by 'Proven Efficacy' and 'Comparable to well-controlled warfarin in the treatment and prevention of recurrent VTE events'. Then followed the claim at issue 'Superior reduction in clinically relevant bleeding and 'Vs. well-controlled warfarin'. The claim at issue was referenced to the Hokusai-VTE Investigators 2013.

The page was designed such that 'Proven Efficacy' and 'Superior Reduction in clinically relevant bleeding' were in upper case and highlighted in blue. These claims were followed by 'Comparable to well-controlled warfarin in the treatment and prevention of recurrent VTE events' and 'Vs. well-controlled warfarin' in smaller black type with no highlighting beneath each respectively.

COMPLAINT

Bayer alleged that similar to point 3 above, this claim was disparaging in breach of Clauses 7.2, 7.4, 7.9, 7.10 and 8.1. It was not clear what 'superior' was compared to. 'Reduction' was versus warfarin but 'superior reduction' indicated that the reduction was greater than some other reduction, implying a head-to-head comparison where one did not exist.

RESPONSE

Daiichi-Sankyo made no separate submission for this point which it covered in point 3 above.

PANEL RULING

The Panel noted its ruling in point 3 above and considered that the position was similar in relation to the VTE claims. The Panel considered that, on balance, the claim 'SUPERIOR REDUCTION IN CLINICALLY RELEVANT BLEEDING' was not misleading or ambiguous as alleged as it did not claim that the difference between Lixiana and warfarin was superior to that seen with other NOACs. The claim 'Vs. well-controlled warfarin' was sufficiently prominent to qualify the claim in question. There was no mention of other NOACs on page 2. The comparisons were all with warfarin. The Panel therefore ruled no breach of Clauses 7.2 and 7.4. The Panel also ruled no breach of Clauses 7.9 and 7.10. The Panel did not consider the claim disparaged Xarelto as alleged and no breach of Clause 8.1 was ruled. Nor did the Panel consider the claim was a hanging comparison. No breach of Clause 7.2 was ruled in this regard.

5 Claims 'Once-daily Lixiana is simple and convenient' and 'Once-daily Lixiana is simple and convenient for patients and prescribers'

The claim 'Once daily Lixiana is simple and convenient' appeared as the heading to page 5 which included a table showing dosing transitions and pill burden (further details appear in Point 7 below).

The claim 'Once daily Lixiana is simple and convenient for patients and prescribers' appeared as the heading to page 3 which set out the dosing regimens for NVAF and VTE and included 'VTE patients should receive heparin for least 5 days before initiating Lixiana'.

COMPLAINT

Bayer alleged that these claims underplayed the inherent complexity and inconvenience of needing 5 days of injected low molecular weight heparin (LMWH) prior to being able to start Lixiana in the VTE population. Many patients were likely to need nurse home visits or to attend clinic in order for this to be possible, or else to be trained on how to self-administer an injection. It was therefore clearly

not justified to suggest this was 'simple' for anyone concerned. The choice of Lixiana dosing was alleged to be far from simple. Multiple factors impacted on dose selection, so much so that a 15mg tablet had to be made commercially available to facilitate dosing transitions despite this dose not being licensed in isolation *per se*. Bayer alleged that Lixiana was not 'simple and convenient' for the patient or the prescriber, and both of the claims were therefore misleading in breach of Clause 7.2 and not capable of substantiation in breach of Clause 7.4. Furthermore, 'simple' was contrary to the SPC in breach of Clause 3.2.

RESPONSE

Daiichi-Sankyo noted that Bayer only referred to the VTE indication for Lixiana as the need for a heparin lead-in did not apply to NVAF patients. Indeed, Bayer had successfully argued the use of the phrase 'one tablet, once daily, simple' in Case AUTH/2537/10/12.

As in that case, the phrase applied to the dosing regimen of Lixiana. On the front of the leavepiece, the claim was followed prominently by 'New ONCE-DAILY Lixiana'. The claim 'Once-daily Lixiana is simple and convenient for patients and prescribers' was on the dosing page. There was no indication generally that Lixiana was simple to use.

The posology of Lixiana was identical regardless of whether the patient was being treated for a VTE event or for prevention of stroke in NVAF. The other factor Xa inhibitors had different posologies depending on their indication.

With regard to Bayer's view that the use of LMWH was inherently complex and inconvenient, Daiichi-Sankyo noted that, like warfarin, heparin and LMWH had been on the market for decades and that their use in hospitals was routine, even mandated as prophylaxis for VTE events. Their use was still recommended in current guidelines (NICE CG92, SIGN 122, NICE TA 354, ESC PE guidelines 2014). Therefore, Daiichi-Sankyo did not shy away from the need for a heparin lead in prior to initiation of Lixiana and this was reiterated four times in the leavepiece. In those patients who had received heparin already, the decision to transition to Lixiana was made simple by the fact there was no further dose transition at initiation unlike other factor Xa inhibitors which required between one week and three weeks of a high dose treatment before reducing to another dose. As stated above, it was important that health professionals realised this difference as they might be under the impression that a similar transition was required for patients started on Lixiana.

The dosing criteria for the most commonly prescribed LMWH such as enoxaparin or dalteparin required a similar dosing adjustment according to body weight and renal function, meaning that these factors would already be known to the prescriber when initiating Lixiana.
Given the need for at least 5 days of heparin lead-in, Daiichi-Sankyo was aware that patients initiated on Lixiana would be those who were likely to have been hospitalised for more severe VTE events such as pulmonary embolism or extensive deep vein thrombosis. These patients were therefore in a hospital environment where the use of heparin was routine.

As for the availability of the 15mg tablet of Lixiana to temporarily protect patients should they need to transition back to warfarin from a 30mg daily dose of Lixiana, Bayer was aware that this regulatory requirement was as a result of the findings at the end of other NOAC trials where patients on the NOAC experienced a nearly 4-fold events increase in stroke and major bleeding due to the period of lack of anticoagulation as patients transitioned to warfarin. (HR 3.72, p=0.004 Actual rate increase 4.7 per 100 Pt-Y for stroke and HR 3.62, p=0.0026 Actual rate increase 5.19 per 100 Pt-Y for major bleeding). Similar increases in events were noted at the end of the apixaban trial. There were no excess of events at the end of the edoxaban ENGAGE-AF study as a result of this transition strategy. None of the other NOACs had a dose licensed to protect patients should they need to transition back to warfarin.

Daiichi-Sankyo always made the statement 'simple and convenient …' in the context of the once-daily dosing of Lixiana, reflective of the posology of Lixiana. Daiichi-Sankyo refuted breaches of Clauses 3.2, 7.2 and 7.4.

PANEL RULING

The Panel noted that the claim 'Simple and convenient for patients and prescribers' appeared as a banner claim at the top of page 1. This appeared to be contrary to Daiichi-Sankyo's submission that 'simple and convenient' was always in the context of once-daily dosing. The claim was followed by 'New once-daily Lixiana (edoxaban) another step ahead'. The second claim was in larger type size than the first claim. Nevertheless there was a claim that Lixiana was simple to use. However, Bayer had not complained about the claim 'Simple and convenient for patients and prescribers'.

The Panel agreed with both companies that Lixiana like other similar medicines was not necessarily simple to use. It noted Daiichi-Sankyo's submission that it was the once-daily dose which meant that Lixiana was simple to use. Page 3 set out the dosing regimen 60mg once-daily (or 30mg once-daily when a reduced dose was needed) for eligible NVAF and VTE patients. This page also referred to the need for pre-treatment for VTE patients with heparin. Page 5 set out the dosing regimens for Lixiana, rivaroxaban, dabigatran and apixaban.

The Panel noted that treatment of eligible NVAF patients with Xarelto was also once-daily and the other two products dabigatran and apixaban were dosed twice daily in this indication.

In VTE Lixiana was once-daily (following heparin pre-treatment) whereas whilst there was no heparin pre-treatment with Xarelto or apixaban there was a dose transition from 15mg twice-daily for 3 weeks to 20mg once-daily for Xarelto and from 10mg twice-daily for

7 days to 5mg twice-daily for apixaban. Dabigatran was 150mg twice-daily after requiring heparin for at least 5 days.

The Panel considered that it was not unreasonable to claim that Lixiana's once-daily dosing regimen was simple and convenient including in VTE once treatment with Lixiana had commenced. The requirement to receive heparin for at least five days before initiating Lixiana in VTE patients was stated on pages 3 and 5. The Panel was concerned that on page 5 the requirement to receive heparin was only visible when, and if, the reader pulled a tab to reveal the VTE dosing regimens. However, on balance, the Panel did not consider that the claims as used on pages 3 and 5 were misleading as alleged, it was sufficiently clear that simple and convenient referred to once-daily dosing. The Panel ruled no breach of Clause 7.2. As such the claims at issue were capable of substantiation and therefore no breach of Clause 7.4 was ruled. Lixiana was used for VTE patients' once-daily after treatment with that product had commenced, ie after at least 5 days' treatment with heparin. The term 'simple' within the context of the claims in question and rulings of no breach of the Code above was not inconsistent with the SPC. The Panel thus ruled no breach of Clause 3.2.

6 Claim and graphic 'Dosing transitions and pill burden in the first 30 days' [VTE]

Page 5 of the leavepiece was headed 'Once-daily Lixiana is simple and convenient' which was followed by 'Dosing transitions and pill burden in the first 30 days of treatment with NOACs for NVAF and VTE'. This was a heading to a graph which compared Lixiana with rivaroxaban, dabigatran and apixaban in relation to dose and number of tablets for NVAF and VTE based on 30 days of treatment. The timescale was from 0 to 6 months. The graphic included dotted lines at 30 days. The pill burden for VTE in the first 30 days of treatment was 30 for Lixiana (60 or 30mg once-daily after ≥5 days of heparin use. Rivaroxaban showed a pill burden of 51, 15mg twice daily for 3 weeks and 20mg (or 15mg) once-daily). Dabigatran was 60 at 150mg or 110mg twice-daily after ≥5 days of heparin use. The pill burden for apixaban was 74. Two x 5mg twice-daily for 7 days followed by 5mg (or 2.5mg) twice-daily followed by 2.5mg twice-daily for prevention.

The page included a tab which when pushed up changed the graphic from a comparison of the pill burden in NVAF to VTE.

COMPLAINT

Bayer alleged that the artwork and numerical claims for VTE were misleading, unsafe and defamatory to its product Xarelto. Calling the point of transition from LMWH to Lixiana 'time zero' was alleged to be misleading and misrepresentative. Time zero should be from the time of diagnosis/initiation of anticoagulation. Starting from the point of switch to Lixiana implied that the first 5 days of anticoagulation were not needed, which was alleged to be misleading in breach of Clause 7.2, unsafe in breach of Clause 7.10 and incompatible with the SPC in breach of Clause 3.2. This was essentially a 'suppressed zero' of the time axis, which specifically breached Clause 7.8. The omission of the first 5 days of injections furthermore downplayed the complexity, inconvenience and discomfort of using Lixiana relative to Xarelto which was pictured alongside. This comparison was thus alleged to be misleading in breach of Clause 7.3, visually non-representative in breach of Clause 7.8 and disparaging of Xarelto in breach of Clause 8.1. Bayer had a further concern over the choice of a 30-days' treatment horizon for the commercial comparison. The Lixiana SPC defined even 'short term treatment' as at least three months' duration. The choice of a 30-day treatment horizon was alleged to thus fail to promote rational prescribing in breach of Clause 7.10 in a manner contradictory to the SPC in breach of Clause 3.2.

Bayer alleged that this clinically-incongruent choice of a 30-day treatment horizon was made in order to exaggerate the difference in pill burden vs other NOACs. Use of a 30 day cut-off made Xarelto appeared to have a pill burden 1.7x heavier than Lixiana (30 vs 51 tablets). In fact, over the minimum recommended treatment span of 90 days, the actual difference was only 1.22x (90 vs 111 tablets), which would be further off-set by the additional 5-10 injections needed for Lixiana had this been honestly represented in the graphic. In summary, the choice of 30 days was alleged to be inaccurate in breach of Clause 7.2; misleading by comparison in breach of Clause 7.3; visually misrepresentative in breach of Clause 7.8; failed to promote rational use of any of the products in breach of Clause 7.10; contrary to the SPC in breach of Clause 3.2 and was defamatory of Xarelto in breach of Clause 8.1. Bayer alleged that overall this constituted a further failure to maintain high standards in breach of Clause 9.1.

RESPONSE

Daiichi-Sankyo submitted that the 30 day pill count remained an important time point for both patients and prescribers when making their choice from the four available NOACs.

At around the 30 day mark, patients typically renewed their prescription. Indeed, some hospitals would provide the initial treatment pack to cover the first month especially for those with complicated regimes.

Studies tracking adherence in the area of anticoagulation as well as other chronic cardiovascular conditions showed a drop-off after the first 30 days. In various studies, treatment frequency and regimen complexity had been shown to have a significant impact on adherence/compliance. An example (Ingersoll *et al* 2008) was provided.

Daiichi-Sankyo submitted that Bayer had presented data showing patterns of use following initiation of rivaroxaban at its ESC satellite symposium (Monday, 31 August 2015) pointing to more relevant VTE persistence data. It could be seen from all the persistence curves that at 30 days, there was a consistent drop in adherence. Daiichi-Sankyo

provided graphs comparing rivaroxaban vs warfarin, NOAC vs VKA and rivaroxaban vs dabigatran for various indications.

As for the time horizon, Daiichi-Sankyo submitted that this was the most fair 'time zero' and clarified at the top of the graphic that the numbers referred to days of NOAC treatment. Had it included the heparin lead-in, the tablet count for 30 days of treatment would be 25 days or less. Instead it made the need for 5 or more days of heparin abundantly clear in the graphic itself as well as in three other instances in the leavepiece.

Daiichi-Sankyo submitted it represented the pill count accurately for each NOAC as per the SPCs at clinically relevant time points, not omitting the need for a heparin lead-in and had not disparaged or defamed Xarelto. Daiichi-Sankyo refuted breaches of Clauses 3.2, 7.2, 7.8 and 8.1.

PANEL RULING

The Panel considered that the page was clear that time zero was the time of initiation of treatment with Lixiana and not when VTE was diagnosed and treatment commenced. The Panel did not accept that the first 5 days of injections had been omitted as alleged, the graph clearly referred to the need for treatment with heparin for Lixiana for VTE and thus it ruled no breach of Clauses 7.3 and 7.8 in relation to Bayer's allegation that this omission downplayed the complexity, inconvenience and discomfort of using Lixiana compared to Xarelto. In that regard, Xarelto was not disparaged and no breach of Clause 8.1 was ruled. The heading to the graph referred to the first 30 days of treatment with NOACs. The graph did not imply that pre-treatment with heparin was not necessary as alleged. The Panel ruled no breach of Clause 7.2 on this point. The Panel consequently ruled no breach of Clauses 7.10 and 3.2 on this point. Nor did the Panel consider that there was a suppressed zero of the time axis as alleged; it was clear that the axis related to the start of treatment with a NOAC. No breach of Clause 7.8 was ruled.

The Panel examined the page in question. It considered that it was misleading and unfair to compare dosing transition and pill burden for 30 days where Lixiana was indicated for at least 3 months ie 90 days, the Lixiana SPC referred to a minimum treatment period of at least 3 months, ie 90 days. It was true that Lixiana had an advantage regarding the number of pills to be taken at either 30 days or 90 days but the difference at 90 days was less than at 30 days. When treating VTE there was an additional burden in that heparin for at least 5 days was also required to treat VTE. It was more complex to treat with heparin than with a tablet.

The Panel noted its comments about the 30 day treatment period above. The Panel considered the graph was misleading in relation to the 30 days and ruled a breach of Clause 7.2. The graph did not give a fair and balanced view of the pill burden and was ruled in breach of Clause 7.8. On balance, the Panel did not consider that the graph failed to promote rational prescribing as alleged and no breach of Clause 7.10 was ruled.

The Panel considered that the 30-day treatment emphasis meant that rational prescribing had not been promoted as the leavepiece did not refer to the treatment with Lixiana as at least 3 months as set out in the SPC. The Panel ruled a breach of Clause 7.10 as alleged. In this regard, the graph was inconsistent with the SPC and a breach of Clause 3.2 was ruled.

The Panel noted its rulings above and considered that in relation to the graph Daiichi-Sankyo had not maintained high standards and a breach of Clause 9.1 was ruled.

Complaint received **23 February 2016**

Case completed **16 May 2016**