CASE AUTH/3010/1/18

BRISTOL-MYERS SQUIBB AND PFIZER v DAIICHI-SANKYO

Promotion of Lixiana

Bristol-Myers Squibb Pharmaceuticals and Pfizer (The Alliance) made a joint complaint about the promotion of Lixiana (edoxaban) by Daiichi-Sankyo. Lixiana was a direct oral anticoagulant (DOAC) of which there were currently four marketed in the UK: edoxaban, rivaroxaban, dabigatran and apixaban. Apixaban (Eliquis) was marketed by the Alliance.

The detailed response from Daiichi-Sankyo is given below.

The Alliance alleged that Daiichi-Sankyo had failed to include important information from the Lixiana summary of product characteristics (SPC) in promotional material. Section 4.4 (Special warnings and precautions for use) included:

> **'Renal function in [nonvalvular atrial fibrillation] NVAF**
>
> **A trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin (see section 5.1). Therefore, edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful evaluation of the individual thromboembolic and bleeding risk.'**

The Alliance further noted that this precautionary wording was unique to Lixiana. Despite the fact that none of the other three DOACs had such wording in their SPCs, there was a consistent, even ubiquitous, omission of any mention of the precautionary wording in any Lixiana promotional material. The Alliance alleged that this misled as to the type and number of patients who might be eligible for Lixiana and misrepresented its risk benefit profile for a significant number of patients who might have a high creatinine clearance.

The Alliance alleged the misleading omission of this precautionary wording in all Lixiana materials but it was particularly notable in two items. The first, a Lixiana 'Initiation Information Guide' stated: 'This booklet contains important summary information designed to help prescribers initiate Lixiana appropriately', specific sections on indications and recommended dose, switching, contraindications, cautions, pregnancy and breastfeeding, hepatic impairment, renal impairment, monitoring, prescribing and dispensing information, storage, missed dose, patient alert card, further information, interactions summary and side-effects. Despite the extremely detailed content there was no mention in any of these sections of the precautionary wording from the SPC about patients with high creatinine clearance levels. This omission was particularly misleading as the 'Cautions' section referred to patients with end stage renal disease. By including information about patients with low creatinine clearance but not important information about patients with high creatinine clearance gave the misleading impression that there were no important considerations for the latter group of patients. The precaution relating to patients with high creatinine clearance was not a trivial matter. Underdosing of patients with atrial fibrillation with anticoagulants could put them at increased risk of serious outcomes such as stroke or systemic embolism. Such adverse outcomes could be life-changing or even fatal.

Similar allegations were made about the second item at issue, a Lixiana 'Practical Guide', was described in the 'Overview' section as 'specifically for prescribers in relation to the use of Lixiana'.

The Alliance refuted Daiichi-Sankyo's assertion that the precautionary wording at issue was in the prescribing information and thus did not need to be included in the body text of the promotional material itself as the Code required the presentation of an accurate, balanced, complete and fair reflection of all the evidence in order to enable the recipient to form their own opinion of the therapeutic value of the medicine. This was particularly the case where matters of patient safety were concerned. When health professionals were encouraged to initiate a particular medicine, or switch patients from one medicine to another, they needed clear information about those patients who might not be suitable for the new medicine. Thus, promotional material which referred to the benefits of a medicine but omitted any warnings, relying instead on the reader referring to the prescribing information, usually placed at a distance at the back of the material, did not present a complete and balanced case regarding a significant proportion of patients. For example, there was a great deal of prominent information on Lixiana, in the 'Practical Guide' and 'Initiation Guide', discussed above, much of which could also be found in the prescribing information. However, Daiichi-Sankyo had also chosen to include this information prominently in the body of the promotional material itself, just as it had always omitted from the body text the precautionary wording at issue. In short, the appearance of the precautionary wording in the prescribing information alone was not adequate. Presentation of the information about a medicine in this way was unbalanced, misleading and potentially dangerous.

The Alliance stated that the other principal pillar of Daiichi-Sankyo's defence of the omission of this important information was to refer to the National Institute for Health and Care Excellence (NICE) technology appraisal of edoxaban TA355 which it selectively quoted as saying 'there is no reason to make differential recommendations based

on creatinine clearance'. However, The Alliance noted that the NICE committee noted the relevant warning at Section 4.4 of the SPC before concluding that if edoxaban was used in accordance with that SPC there was no reason to make differential recommendations based on creatinine clearance.

The Alliance stated that it was therefore clear that the Committee considered that this wording, contained within the SPC, was an adequate warning but that the clinician needed to take this into consideration before deciding to prescribe. It was on this basis that the Committee decided that it did not need to issue any additional differential recommendations. The Alliance agreed with NICE that edoxaban should be used, and therefore promoted, in accordance with its SPC, which would therefore include any appropriate warnings and precautions.

The Alliance stated that whilst not relevant to the regulatory guidance issued about the use of Lixiana in the UK, it was reflective of the clinical importance of this UK SPC warning statement that in the USA the Food and Drug Administration (FDA) included these considerations as a contraindication black box warning in the Lixiana prescribing information. Details were provided.

In summary, the Alliance stated that the considered and ubiquitous omission from all promotional material of a prominent precautionary statement, found in the SPC, about the use of Lixiana in patients with high creatinine clearance, potentially placed a significant number of patients at risk of stroke or systemic embolism in breach of the Code.

The Panel noted that Lixiana was indicated for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).

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

The Panel noted the relevant warning Section 4.4 of the Lixiana SPC.

The Panel further noted that a subgroup analysis based on renal function which used 3 categories of creatinine clearance (CrCl) was discussed in the NICE technology appraisal guidance on edoxaban for preventing stroke and systemic embolism in people with NVAF which stated that the subgroup analysis across three categories (normal renal function, mild renal impairment and moderate renal impairment) 'suggested that renal function had a significant impact on the efficacy of edoxaban compared to warfarin (p=0.0042)'. The hazard ratios for the primary efficacy endpoint (prevention of stroke or systemic embolic event) were 0.68 (95% CI 0.54-0.85) and 0.86 (95% CI 0.63-1.17) for patients with mild to moderate renal impairment. In contrast the relative risk of stroke or systemic embolic event was higher with edoxaban than with warfarin in patients with normal renal function (HR 1.31, 95% CI 0.96-1.79). The guidance noted the company's view that these results should be treated with caution because a variety of factors including an unusually low event rate in the warfarin group and the lack of randomisation within the sub-groups could have contributed towards the result. The NICE guidance (Section 4.6) noted evidence that the trend towards decreasing efficacy of edoxaban with increasing creatinine clearance was likely to be because with better renal function edoxaban was removed by the kidneys more quickly leading to a reduction in treatment effect. Evidence was also submitted that this might apply to all newer anticoagulants but data needed to be re-evaluated to confirm this. Evidence was provided to NICE that the proportion of people with good renal function measured by creatinine clearance who would be eligible for treatment with edoxaban was in the region of 5-10% and that these were often younger people. The NICE committee noted the relevant warning at Section 4.4 of the SPC before concluding that if edoxaban was used in accordance with that SPC there was no reason to make differential recommendations based on creatinine clearance. The Panel noted that the relevant clinical data was also discussed at Section 5.1 Pharmacodynamic properties, of the Lixiana SPC which showed event rate data for 6 creatinine clearance sub-groups. The Panel noted that the Lixiana SPC stated in a Section 4.2 under the sub-heading Special populations, assessment of renal function, that renal function should be assessed in all patients by calculating creatinine clearance prior to initiation of treatment with Lixiana, *inter alia*, when deciding on the use of Lixiana in patients with increased creatinine clearance.

The Panel noted that a section on page 2 of the six page Lixiana Initiation Information Guide headed 'CAUTIONS' stated that the use of Lixiana was not recommended in patients with end stage renal disease (ESRD) (CrCl <15ml/min or on dialysis). On the following page in a section headed renal impairment it stated that in patients with mild renal impairment the recommended Lixiana dose was 60mg once daily, in patients with moderate or severe renal impairment the recommended dose was 30mg once daily and repeated that in patients with ESRD or on dialysis Lixiana was not recommended. It further stated in a subsequent section headed 'Monitoring' that renal function should be monitored before treatment and when clinically indicated during treatment. There was no reference in the body of the booklet to the SPC warning at issue. The Panel noted Daiichi-Sankyo's submission that the warning was not included within the renal impairment section as there was no recommendation for dose alteration in patients with high creatinine clearance. The Panel noted the comments about the nature of the relevant subgroup analysis in the NICE guidance. The Panel noted that based on this data the regulators had decided to include a special warning about decreased efficacy in patients with high creatinine clearance in the SPC. The SPC

clearly stated that edoxaban should only be used in those patients after a careful evaluation of the individual thromboembolic and bleeding risk. The Panel considered that the warning in question did more than 'encourage' prescribers to undertake a careful evaluation, as stated by Daiichi-Sankyo; the warning stated that edoxaban *should only* be used after a careful evaluation of the individual's thromboembolic and bleeding risk (emphasis added), thereby implying in the Panel's view that such an evaluation was a requirement in this patient population. The Panel noted the stated purpose of the booklet in question to help prescribers initiate Lixiana appropriately and considered that failure to include the special warning was misleading and did not encourage the rational use of the medicine. In the Panel's view it was not sufficient to rely on the prescribing information at the back of the guide to provide the warning about the use of Lixiana and the trend towards the decreasing efficacy in patients with NVAF and high creatinine clearance. Material had to be capable of standing alone with regard to the requirements of the Code and could not rely on qualification in either prescribing information or a footnote. The Panel noted the Alliance's submission about the potential life-changing or even fatal consequences of failing to undertake such an evaluation in the relevant patient population. Breaches of the Code were ruled. The Panel considered that Daiichi-Sankyo had failed to maintain high standards and a breach was ruled. The breaches were upheld upon appeal by Daiichi-Sankyo.

In making these rulings the Appeal Board noted that the FDA had contraindicated the use of Lixiana in this group of patients and noted Daiichi-Sankyo's submission that the EMA had assessed the data differently. Nevertheless there was a warning about use in a patient population with normal kidney function which the Appeal Board considered was unusual. Both items at issue referred readers to the SPC for full prescribing information. The Appeal Board considered that prescribers would not necessarily expect patients with high creatinine clearance and thus normal kidney function to be at risk when prescribing a DOAC for NVAF; it was counter intuitive. It was therefore even more important that the SPC warning in question was drawn to their attention, particularly as Lixiana was the only DOAC that had this specific warning. Other warnings from the SPC were included in the main body of the Initiation Information Guide, including in the Appeal Board's view special warnings and precautions with less strong wording and to omit the warning at issue downplayed its relative importance. The Appeal Board considered that given the nature of the warning it was paramount that it appeared prominently in the body of the item at issue.

The Appeal Board thought it odd that, according to the Daiichi-Sankyo representatives, its field force had been trained on the warning at issue yet the company had omitted the warning from the body of the materials.

In relation to the 19 page Lixiana 'Practical Guide', the Panel noted its general comments above about the warning at Section 4.4 of the SPC, Section 4.2 of the SPC, including comments about the relevant data in the NICE guidance and the prescribing information and considered that they applied here. The Panel noted that the Lixiana Practical Guide covered more matters than the Initiation Information Guide considered above and included discussion of efficacy and safety issues including patients at higher risk of bleeding and special patient populations. The Panel considered that failure to include the special warning at issue, particularly considering there was a page dedicated to special patient populations, was misleading and did not encourage the rational use of the medicine. Breaches of the Code were ruled. The Panel considered that Daiichi-Sankyo had failed to maintain high standards and a breach of the Code was ruled. The breaches were upheld upon appeal by Daiichi-Sankyo.

In making these rulings, the Appeal Board considered that its comments above applied equally to this item. The Appeal Board also noted that the Practical Guide covered more matters than the Initiation Information Guide and included discussion of efficacy and safety issues including patients at higher risk of bleeding and special patient populations. There was a page dedicated to special patient populations and the missing information appeared in the Lixiana SPC under the heading special populations.

The Panel noted the comments in the NICE guidance about the size of the patient population with good renal function (measured by creatinine clearance) who would be eligible for treatment with edoxaban was in the region of 5-10%. The Panel further noted the trend towards decreasing efficacy of edoxaban with increasing creatinine clearance and the consequences of such and considered that Daiichi-Sankyo's failure to include the warning meant that it had potentially put those patients' safety at risk. The Panel considered that patient safety was of the utmost importance and Daiichi-Sankyo's failure in this regard brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled in relation to each item. This was upheld on appeal by Daiichi-Sankyo.

The Appeal Board noted its comments and rulings of breaches of the Code including a breach of Clause 2. The Appeal Board considered that Daiichi-Sankyo's actions had meant that prescribers had been provided with material that failed to highlight an important patient safety consideration and consequently patients might have been put at risk. This was totally unacceptable. The Appeal Board noted that the NHS guidance on the use of DOACs in NVAF provided by the Alliance made no reference to the warning at issue. Consequently, the Appeal Board decided, in accordance with Paragraph 10.6 of the Constitution and Procedure, to require Daiichi-Sankyo to issue a corrective statement to all recipients of the material at issue. In addition, the Appeal Board considered that given the items broad dissemination including that in the Appeal Board's view it was more likely than not that this material would have been shared by prescribers with colleagues, the Appeal Board considered that

the corrective statement should also be sent to relevant UK prescribers. The corrective statement should refer to the case report. Under Paragraph 10.6 details of the proposed content and mode and timing of dissemination of the corrective statement must be provided to the Appeal Board for approval prior to use.

In addition, the Appeal Board decided, in accordance with Paragraph 10.3, to require Daiichi-Sankyo to take steps to recover the material from those who had received it; written details of the action taken must be provided to the Appeal Board. This should be included in the corrective statement. [The corrective statement, which was agreed by the Appeal Board prior to use, appears at the end of this report.]

Bristol-Myers Squibb Pharmaceuticals Limited and Pfizer Limited (The Alliance) made a joint complaint about the promotion of Lixiana (edoxaban) by Daiichi-Sankyo UK Ltd. Lixiana was a direct oral anticoagulant (DOAC) of which there were currently four marketed in the UK: edoxaban, rivaroxaban, dabigatran and apixaban. Apixaban (Eliquis) was jointly marketed by Bristol-Myers Squibb and Pfizer (the Alliance).

COMPLAINT

The Alliance noted that Section 4.4 (Special warnings and precautions for use) of the current Lixiana summary of product characteristics (SPC) contained the following:

> 'Renal function in [nonvalvular atrial fibrillation] NVAF
>
> A trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin (see section 5.1). Therefore, edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful evaluation of the individual thromboembolic and bleeding risk.'

The Alliance further noted that this precautionary wording was unique to Lixiana. Despite the fact that none of the other three DOACs had such wording in their SPCs, there was a consistent, even ubiquitous, omission of any mention of the precautionary wording in any Lixiana promotional material. The Alliance alleged that this misled as to the type and number of patients who might be eligible for Lixiana and misrepresented its risk benefit profile for a significant number of patients who might have a high creatinine clearance.

The Alliance stated that there was a misleading omission of this precautionary wording in all Lixiana materials but it was particularly notable in two items, the first of which was a Lixiana 'Initiation Information Guide' (ref EDX/16/0171) which described itself as follows: 'This booklet contains important summary information designed to help prescribers initiate Lixiana appropriately'. The booklet contained specific sections on indications and recommended dose, switching, contraindications, cautions, pregnancy and breastfeeding, hepatic impairment, renal impairment, monitoring, prescribing and dispensing information, storage, missed dose, patient alert card, further information, interactions summary and side-effects. Despite the extremely detailed content there was no mention in any of these sections of the precautionary wording from the SPC about patients with high creatinine clearance levels. This omission was particularly misleading as the 'Cautions' section referred to patients with end stage renal disease. By including information about patients with low creatinine clearance but not important information about patients with high creatinine clearance gave the misleading impression that there were no important considerations for the latter group of patients. However, the precaution relating to patients with high creatinine clearance was not a trivial matter. Underdosing of patients with atrial fibrillation with anticoagulants could put them at increased risk of serious outcomes such as stroke or systemic embolism. Such adverse outcomes could be life-changing or even fatal.

The second item at issue was a Lixiana 'Practical Guide' (ref EDX/15/0091(4)). In its 'Overview' section it described itself as 'specifically for prescribers in relation to the use of Lixiana' and listed the following section headings: indications, summary of efficacy and safety, dosing recommendations and dose reductions, information on switching patients to or from Lixiana, populations at potentially higher risk of bleeding, special patient populations, temporary discontinuation, perioperative management, overdose, management of bleeding complications, coagulation testing, patient alert card. However, despite this detailed content on the practical considerations on the use of Lixiana, and reference to patients with low creatinine clearance, there was no mention of the precautionary wording about patients with high creatinine clearance.

The Alliance stated that during inter-company dialogue, Daiichi-Sankyo, in defence of its omission of this information, had asserted that the precautionary wording at issue was in the prescribing information and thus did not need to be included in the body text of the promotional material itself. The Alliance refuted this assertion as the Code required the presentation of an accurate, balanced, complete and fair reflection of all the evidence in order to enable the recipient to form their own opinion of the therapeutic value of the medicine. This was particularly the case where matters of patient safety were concerned. When health professionals were encouraged to initiate a particular medicine, or switch patients from one medicine to another, they needed clear information about those patients who might not be suitable for the new medicine. Thus, promotional material which referred to the benefits of a medicine but omitted any warnings, relying instead on the reader referring to the prescribing information, usually placed at a distance at the back of the material, did not present a complete and balanced case regarding a significant proportion of patients. For example, there was a great deal of prominent information on Lixiana, in the 'Practical Guide' and 'Initiation Guide', discussed above, much of which could also be found in the prescribing information. However, Daiichi-Sankyo had also chosen to include this information

prominently in the body of the promotional material itself, just as it had always omitted from the body text the precautionary wording at issue. In short, the appearance of the precautionary wording in the prescribing information alone was not adequate. Presentation of the information about a medicine in this way was unbalanced, misleading and potentially dangerous.

The Alliance stated that when encouraging health professionals to initiate treatment with a medicine, there was an obligation to point out to them specifically if there was a significant group of patients where particular caution should be exercised. In this instance, Daiichi-Sankyo had failed to do so with appropriate prominence in any of its materials, even ones which purported to give detailed and specific guidance on the initiation and use of its medicine.

The Alliance stated that the other principal pillar of Daiichi-Sankyo's defence of the omission of this important information was to refer to the National Institute for Health and Care Excellence (NICE) technology appraisal of edoxaban TA355 which it selectively quoted as saying 'there is no reason to make differential recommendations based on creatinine clearance'. However, The Alliance noted that the full wording was:

> 'It [The Committee] also noted the summary of product characteristics which states that, in people with non valvular atrial fibrillation and high creatinine clearance, edoxaban should only be used after careful evaluation of a person's thromboembolic and bleeding risk. The Committee concluded that if edoxaban is used in accordance with the summary of product characteristics, there is no reason to make differential recommendations based on creatinine clearance.'

The Alliance stated that it was therefore clear that the Committee considered that this wording, contained within the SPC, was an adequate warning but that the clinician needed to take this into consideration before deciding to prescribe. It was on this basis that the Committee decided that it did not need to issue any additional differential recommendations. The Alliance agreed with NICE that edoxaban should be used, and therefore promoted, in accordance with its SPC, which would therefore include any appropriate warnings and precautions.

The Alliance stated that whilst not relevant to the regulatory guidance issued about the use of Lixiana in the UK, it was reflective of the clinical importance of this UK SPC warning statement that in the USA the Food and Drug Administration (FDA) had included these considerations as a contraindication black box warning in the Lixiana prescribing information:

'REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CRCL >95 ML/MIN: SAVAYSA should not be used in patients with CrCL >95mL/min. In the ENGAGE AF-TIMI 48 study, nonvalvular atrial fibrillation patients with CrCL >95mL/min had an increased rate of ischemic stroke with SAVAYSA 60mg once daily compared to patients treated with warfarin. In these patients another anticoagulant should be used.'

In summary, the Alliance stated that the considered and ubiquitous omission from all promotional material of a prominent precautionary statement, found in the SPC, about the use of Lixiana in patients with high creatinine clearance, potentially placed a significant number of patients at risk of stroke or systemic embolism and represented a clear breach of Clauses 7.2, 7.10, 9.1 and 2.

RESPONSE

Daiichi-Sankyo stated that the edoxaban SPC listed one of the therapeutic indications for Lixiana as 'prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors'.

In its complaint, the Alliance had quoted a paragraph from Section 4.4 (Special warnings and precautions for use) of SPC:

> 'Renal function in NVAF
>
> A trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin (see section 5.1). Therefore, edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful evaluation of the individual thromboembolic and bleeding risk.'

The Alliance had incorrectly alleged that this precautionary wording had been consistently omitted from all Lixiana promotional materials, including EDX/16/0171 and EDX/15/0091(4). The prescribing information which formed a part of all Lixiana promotional materials contained clear details of this precaution (as required by Clauses 4.1 and 4.2):

> 'Renal function and NVAF: A trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin. Edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful benefit risk evaluation.'

This wording was entirely consistent with Section 4.4 of the Lixiana SPC.

Daiichi-Sankyo stated that it had withdrawn the Lixiana Initiation Information Guide for prescribers before it received the complaint from the Alliance and this was communicated to the Alliance in Daiichi-Sankyo UK's initial response letter on 14 November 2017. The item was not specifically discussed during the face-to-face meeting. Subsequently, the Alliance stated in its response on 5 January 2018 that it considered 'all other matters raised in previous correspondence but not discussed at this [face-to-face] meeting to have been resolved'. Daiichi-Sankyo was thus surprised that the Alliance had specifically named this material in its complaint as it knew it had been withdrawn and had stated that it considered the matter resolved.

The Alliance had alleged that not referring to patients with high creatinine clearance in the main body of text in the Initiation Information Guide was misleading because patients with low creatinine clearance were discussed. Daiichi-Sankyo did not agree with this reasoning. The mention of patients with low creatinine clearance (ie moderate or severe renal impairment) was necessary because a dose adjustment was required for patients with creatinine clearance between 15-50ml/min, as per Section 4.2 (Posology and method of administration) of the Lixiana SPC:

> 'Renal impairment
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> In patients with mild renal impairment (CrCL >50 – 80mL/min), the recommended dose is 60 mg Lixiana once daily.
>
> In patients with moderate or severe renal impairment (CrCL 15 – 50mL/min), the recommended dose is 30mg Lixiana once daily (see section 5.2).
>
> In patients with end stage renal disease (ESRD) (CrCL <15mL/min) or on dialysis, the use of Lixiana is not recommended (see sections 4.4 and 5.2).'

Daiichi-Sankyo stated that it was entirely proper and rational that the dose reduction criteria for patients with renal impairment should be mentioned in the main text of the Initiation Information Guide which was intended to help prescribers initiate Lixiana.

Conversely, there was no recommendation for dose alteration in the Lixiana SPC for patients with high creatinine clearance, which was why this group had not been given the same prominence in the main text as patients with renal impairment. Patients with high creatinine clearance were not renally impaired and had normal functioning kidneys. There was, therefore, no requirement to discuss patients with high creatinine clearance in conjunction with discussion around dose modification for patients with renal impairment, as they were very different patient groups. Patients with high creatinine clearance were instead discussed in the prescribing information of the Initiation Information Guide. Daiichi-Sankyo also noted that the front page of the Guide expressly and clearly instructed health professionals to consult the prescribing information and SPC for full information thus:

> 'For UK healthcare professionals only in relation to the use of LIXIANA.
> Prescribing information can be found on the back cover.
> For additional prescriber and patient resources please visit www.lixiana.co.uk.
> Please consult the Summary of Product Characteristics (SmPC) for full prescribing information.'

Daiichi-Sankyo noted that the Alliance had also complained that there was no mention in the Lixiana Practical Guide for prescribers of the precautionary wording from the SPC about high creatinine clearance, despite there being discussion of patients with low creatinine clearance. The justification that Daiichi-Sankyo had given for the Initiation Information Guide also applied to this material. Additionally, in the Practical Guide, the discussion of patients with renal impairment was within a section discussing groups at increased risk of bleeding on page 15. The wording on page 15 indicated:

> 'Several groups of patients are at increased risk of bleeding and should be carefully monitored for signs and symptoms of bleeding complications. Any treatment decision must be based on careful assessment of the treatment benefit against risk of bleeding.'

Patients with high creatinine clearance were not at increased risk of bleeding with Lixiana, and therefore discussion of this group would not be suitable within this section. Patients with high creatinine clearance were referred to in the prescribing information on page 20.

The front page of the Practical Guide also had the clear statement:

> 'Prescribing information can be found on the back cover.'

The following page which was an overview of the material stated:

> 'Please consult the Summary of Product Characteristics (SmPC) for full prescribing information.'

Thus, health professionals were expressly and clearly instructed to consult the prescribing information and SPC for full information.

Given health professionals' responsibility to familiarise themselves with product information if not already so familiar, Daiichi-Sankyo stated that it would expect all health professionals reviewing the above materials to follow the clear instruction to refer to the prescribing information or SPC if they needed to, in order to become properly acquainted with the product. Daiichi-Sankyo disagreed with the inference made by the Alliance that the prescribing information was not sufficiently prominent to come to the prescriber's attention and/or that prescribers would not refer to it because it was 'usually placed at a distance at the back of the material'. The prescribing information in both documents was easy to locate on the last page, so very accessible for anyone seeking to review it. Prescribers would recognise the importance of the clear instructions to refer to it for more detailed information.

Daiichi-Sankyo stated that Lixiana had been evaluated by NICE in Technology Appraisal 355 (TA355). The Alliance had stated in its letter of complaint that Daiichi-Sankyo UK had selectively quoted aspects of TA355 as part of its defence. Daiichi-Sankyo noted that the passage from TA355 in question was not quoted in any promotional materials; rather it was quoted by Daiichi-Sankyo UK during inter-company dialogue. In the initial written response to the Alliance on 14 November 2017, Daiichi-Sankyo UK stated:

'I will draw your attention to the National Institute for Health and Care Excellence (NICE) Technology Appraisal 355 (TA355), titled "Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation". Section 4.6 of this document discusses patients with high creatinine clearance, and states, "The Committee concluded that if edoxaban is used in accordance with the summary of product characteristics, there is no reason to make differential recommendations based on creatinine clearance."'

Daiichi-Sankyo did not view this as a selective quote, as it was, in fact, the concluding statement of Section 4.6 of TA355, and adequately summarised the decision made by the Committee on that topic. It was clear that in the context of patients with high creatinine clearance and NVAF, NICE did not believe that differential recommendations were required. While Daiichi-Sankyo UK drew on NICE recommendations when developing promotional materials, it stressed that it had never advocated any use of Lixiana that was inconsistent with the SPC.

Daiichi-Sankyo noted that the Alliance had referred to the American FDA label for Lixiana in its complaint. However, as the Alliance had also noted, the FDA label wording was not relevant to UK regulatory guidance, and it was therefore irrelevant to this discussion about compliance with the Code. The SPC did not include any contraindication for Lixiana in patients with NVAF and high creatinine clearance.

The Alliance had alleged that the Initiation Information Guide and the Practical Guide, as well as other Lixiana promotional materials in general were unbalanced, misleading and potentially dangerous. For the reasons given above, Daiichi-Sankyo refuted those allegations.

The Alliance had alleged a breach of Clause 7.2. Daiichi-Sankyo did not agree that the materials were misleading; they were sufficiently complete to enable prescribers to form their own opinions on the therapeutic value of Lixiana. Indeed, the prescribing information encouraged prescribers to carry out a careful benefit risk evaluation in this group of patients, consistent with the SPC. On this basis, Daiichi-Sankyo denied a breach of Clause 7.2.

The Alliance had alleged a breach of Clause 7.10 but did not clearly explain why. Lixiana promotional materials encouraged the rational use of the medicine, as evidenced by the inclusion of precautionary wording in the prescribing information. There were no exaggerated or all-embracing claims in the materials and all claims about Lixiana's properties could be substantiated. Daiichi-Sankyo denied a breach of Clause 7.10.

Further, Daiichi-Sankyo did not believe that high standards had not been maintained, or that it had brought discredit to or reduced confidence in the pharmaceutical industry, therefore it denied breaches of Clauses 9.1 and 2.

Daiichi-Sankyo stated that EDX/16/0171 was certified by two people – a registered medical practitioner (Qualification MBBS), and a non-medical signatory who was a senior official of Daiichi-Sankyo UK. The certificate was provided. This material was disseminated as hard copy by representatives to health professionals. The audience were junior doctors, pharmacists, cardiologists, haematologists, geriatricians, stroke physicians, respiratory physicians and general medical physicians.

Daiichi-Sankyo stated that EDX/15/0091(4) was certified by a registered medical practitioner (Qualifications BMedSci(Hons), BM BS, DRCOG, MRCGP). The certificate was provided. This material was disseminated as hard copy and by email to health professionals. In responding to this complaint, Daiichi-Sankyo UK had learned that an administrative error had regrettably led to the registered medical practitioner's name not being notified to the PMCPA and MHRA in advance. Corrective actions had been put in place and Daiichi-Sankyo would separately contact the Authority with further details of a voluntary disclosure in this regard.

PANEL RULING

The Panel noted that Lixiana was indicated for the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA). The Panel noted that the Alliance was concerned that there was a misleading omission of precautionary SPC wording with regard to Lixiana (edoxaban) use in patients with NVAF and high creatinine clearance in all Lixiana materials and referred to two items, the Lixiana 'Initiation Information Guide' (ref EDX/16/0171) and the Lixiana 'Practical Guide' (ref EDX/15/0091(4)).

The Panel noted Daiichi-Sankyo's submission that during inter-company dialogue it had informed the Alliance in a letter dated 14 November that the Lixiana 'Initiation Information Guide' (ref EDX/16/0171) had already been withdrawn and thus considered that the complaint was resolved in relation to this item. In the Panel's view that material had been withdrawn prior to and wholly independently of matters raised in subsequent inter-company dialogue did not mean that such intercompany dialogue had been successful. In addition, the Panel noted that in its letter dated 14 November Daiichi-Sankyo stated that it reserved the right to use substantially similar materials. The Panel noted that the Alliance minutes of the face to face meeting held on 8 December referred to promotional materials including, *inter alia*, EDX/16/0171 in relation to the subject matter of the present complaint. The Panel further noted that Daiichi-Sankyo's minutes of the meeting stated that this matter was not agreed. The Panel therefore considered that intercompany dialogue had not resolved the matter with regard to the Lixiana 'Initiation Information Guide' and the item would therefore be considered by the Panel.

The Panel considered that whether a special warning or precaution needed to be referred to in material depended on a consideration of all of the

circumstances including the nature of the warning/ precaution, the therapy area and the content and intended use of the material.

The Panel noted that Section 4.4 of the Lixiana SPC, Special warnings and precautions for use, stated under the sub heading Renal function in NVAF:

> 'A trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin (see section 5.1). Therefore, edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful evaluation of the individual thromboembolic and bleeding risk. Assessment of renal function: CrCL should be monitored at the beginning of the treatment in all patients and afterwards when clinically indicated (see section 4.2).'

The Panel noted that a subgroup analysis based on renal function which used 3 categories of creatinine clearance (CrCl) was discussed in the NICE technology appraisal guidance on edoxaban for preventing stroke and systemic embolism in people with NVAF which stated that the subgroup analysis across three categories (normal renal function, mild renal impairment and moderate renal impairment) 'suggested that renal function had a significant impact on the efficacy of edoxaban compared to warfarin (p=0.0042)'. The hazard ratios for the primary efficacy endpoint (prevention of stroke or systemic embolic event) were 0.68 (95% CI 0.54-0.85) and 0.86 (95% CI 0.63-1.17) for patients with mild to moderate renal impairment. In contrast the relative risk of stroke or systemic embolic event was higher with edoxaban than with warfarin in patients with normal renal function (HR 1.31, 95% CI 0.96-1.79). The guidance noted the company's view that these results should be treated with caution because a variety of factors including an unusually low event rate in the warfarin group and the lack of randomisation within the sub-groups could have contributed towards the result. Section 4.6 of the guidance (Consideration of the evidence, Clinical effectiveness) noted evidence that the trend towards decreasing efficacy of edoxaban with increasing creatinine clearance was likely to be because with better renal function edoxaban was removed by the kidneys more quickly leading to a reduction in treatment effect. Evidence was also submitted that this might apply to all newer anticoagulants but data needed to be re-evaluated to confirm this. Evidence was provided to NICE that the proportion of people with good renal function measured by creatinine clearance who would be eligible for treatment with edoxaban was in the region of 5-10% and that these were often younger people. The NICE committee noted the relevant warning at Section 4.4 of the SPC before concluding that if edoxaban was used in accordance with that SPC there was no reason to make differential recommendations based on creatinine clearance. The Panel noted that the relevant clinical data was also discussed at Section 5.1 Pharmacodynamic properties, of the Lixiana SPC which showed event rate data for 6 creatinine clearance sub-groups. The Panel noted that the Lixiana SPC stated in a Section 4.2 under the sub-heading Special populations, assessment of renal function, that renal function should be assessed in all patients by calculating creatinine clearance prior to initiation of treatment with Lixiana, *inter alia*, when deciding on the use of Lixiana in patients with increased creatinine clearance.

The Panel noted that the Lixiana Initiation Information Guide was a 6 page booklet containing important summary information designed to help prescribers initiate Lixiana appropriately including under the following headings: switching, contraindications, cautions, pregnancy and breast feeding, hepatic impairment, renal impairment and monitoring. The Panel noted that a section on page 2 headed 'CAUTIONS' stated that the use of Lixiana was not recommended in patients with end stage renal disease (ESRD) (CrCl <15ml/min or on dialysis). On the following page in a section headed renal impairment it stated that in patients with mild renal impairment the recommended Lixiana dose was 60mg once daily, in patients with moderate or severe renal impairment the recommended dose was 30mg once daily and repeated that in patients with ESRD or on dialysis Lixiana was not recommended. It further stated in a subsequent section headed 'Monitoring that renal function should be monitored before treatment and when clinically indicated during treatment'. There was no reference in the body of the booklet to the SPC warning at issue. The Panel noted Daiichi-Sankyo's submission that the warning was not included within the renal impairment section as there was no recommendation for dose alteration in patients with high creatinine clearance. The Panel noted the comments about the nature of the relevant subgroup analysis in the NICE guidance. The Panel noted that based on this data the regulators had decided to include a special warning about decreased efficacy in patients with high creatinine clearance in the SPC. The SPC clearly stated that edoxaban should only be used in those patients after a careful evaluation of the individual thromboembolic and bleeding risk. The Panel considered that the warning in question did more than 'encourage' prescribers to undertake a careful evaluation, as stated by Daiichi-Sankyo; the warning stated that edoxaban **should only** be used after a careful evaluation of the individual's thromboembolic and bleeding risk (emphasis added), thereby implying in the Panel's view that such an evaluation was a requirement in this patient population. The Panel noted the stated purpose of the booklet in question to help prescribers initiate Lixiana appropriately and considered that failure to include the special warning was misleading and did not encourage the rational use of the medicine. In the Panel's view it was not sufficient to rely on the prescribing information at the back of the guide to provide the warning about the use of Lixiana and the trend towards the decreasing efficacy in patients with NVAF and high creatinine clearance. Material had to be capable of standing alone with regard to the requirements of the Code and could not rely on qualification in either prescribing information or a footnote. The Panel noted the Alliance's submission about the potential life-changing or even fatal consequences of failing to undertake such an evaluation in the relevant patient population. A breach of Clauses 7.2 and 7.10 was ruled. The Panel considered that Daiichi-Sankyo had failed to

maintain high standards and a breach of Clause 9.1 was ruled.

The Panel noted that the second item at issue was a 19 page booklet entitled Lixiana 'Practical Guide' for prescribers in relation to the use of Lixiana. It included information on, *inter alia*, indications, summary of efficacy and safety, dosing recommendations, dose reductions, populations at potentially higher risk of bleeding, and special patient populations.

The Panel noted its general comments above about the warning at Section 4.4 of the SPC, Section 4.2 of the SPC, including comments about the relevant data in the NICE guidance and the prescribing information and considered that they applied here. The Panel noted that based on the data discussed in the NICE guidance the regulators had decided to include a special warning about decreased efficacy in patients with high creatinine clearance in the SPC. The Panel considered that the warning in question did more than 'encourage' prescribers to undertake a careful evaluation, as stated by Daiichi-Sankyo; the warning stated that edoxaban **should only** be used after a careful evaluation of the individual's thromboembolic and bleeding risk (emphasis added), thereby implying in the Panel's view that such an evaluation was a requirement. The Panel noted that the Practical Guide covered more matters than the Initiation Information Guide considered above and included discussion of efficacy and safety issues including patients at higher risk of bleeding and special patient populations. The Panel noted the Alliance's submission about the potential life-changing or even fatal consequences of failing to undertake such an evaluation in the relevant patient population. The Panel considered that failure to include the special warning at issue, particularly considering there was a page dedicated to special patient populations, was misleading and did not encourage the rational use of the medicine. A breach of Clauses 7.2 and 7.10 were ruled. The Panel considered that Daiichi-Sankyo had failed to maintain high standards and a breach of Clause 9.1 was ruled.

The Panel noted the comments in the NICE guidance about the size of the patient population with good renal function (measured by creatinine clearance) who would be eligible for treatment with edoxaban was in the region of 5-10%. The Panel further noted the trend towards decreasing efficacy of edoxaban with increasing creatinine clearance and the consequences of such and considered that Daiichi-Sankyo's failure to include the warning meant that it had potentially put those patients' safety at risk. The Panel considered that patient safety was of the utmost importance and Daiichi-Sankyo's failure in this regard brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled in relation to each item.

APPEAL BY DAIICHI-SANKYO

Daiichi-Sankyo stated that it remained committed to the ethical promotion of medicines and to adhering to the Code. Patient safety was a primary concern for all staff. Daiichi-Sankyo appealed all the rulings of breaches of the Code in relation to the Lixiana Initiation Information Guide and the Practical Guide.

Daiichi-Sankyo submitted that the Initiation Information Guide had already been withdrawn from circulation prior to the Alliance's initial complaint and the Alliance had been made aware of this during intercompany dialogue on 14 November 2017. The notification from Daiichi-Sankyo head office to the field to withdraw all promotional materials as a result of an update to the prescribing information was made in August 2017. The item was not discussed during a face-to-face meeting between the Alliance and Daiichi-Sankyo as it was considered to have been resolved.

Daiichi-Sankyo submitted that it was not appropriate for the Panel to rule upon this historic and withdrawn material. Withdrawn materials had not been considered when complaints had been made in other cases and therefore Daiichi-Sankyo did not understand the basis for considering them in this case. Daiichi-Sankyo appealed breaches of Clauses 7.2, 7.10, 9.1 and 2 in relation to this material, on the basis that it was withdrawn prior to the initial complaint. It was unclear the basis upon which the Panel could consider material which was withdrawn prior to the initial complaint being made.

Notwithstanding the above, Daiichi-Sankyo submitted that if the Appeal Board decided that the Initiation Information Guide was appropriately considered as part of the complaint, all breaches related to this material were appealed in any event for the reasons set out below.

Daiichi-Sankyo submitted that the omitted wording from the material at issue did not cause patient safety issues. In Section 4.4 of the edoxaban SPC, under the subheading 'Renal function in NVAF [Nonvalvular atrial fibrillation]' it stated that 'A trend towards decreasing efficacy with increasing creatinine clearance [CrCl] was observed for edoxaban **compared to well-managed warfarin** (see section 5.1). Therefore, edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful evaluation of the individual thromboembolic and bleeding risk,' (emphasis added).

Daiichi-Sankyo submitted that the decreasing efficacy trend described in the first sentence was for edoxaban compared to well-managed warfarin. It did not describe a trend in edoxaban's absolute efficacy. The second sentence began with the word 'Therefore …' indicating that the second sentence directly related to the description of the comparison in the previous sentence. The statement that edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful evaluation of the individual thromboembolic and bleeding risk, was linked to a description of the efficacy trend when edoxaban and well-managed warfarin were compared, not to the absolute efficacy of edoxaban when viewed in isolation.

Daiichi-Sankyo submitted that Table 5 of the edoxaban SPC showed that in the ENGAGE AF-TIMI 48 study, there was a trend to a decreasing annual

rate of ischaemic stroke/systemic embolic events (SEE) associated with a rise in creatinine clearance in NVAF patients taking edoxaban. The absolute event rate decreased from 1.89%/year in NVAF patients with CrCl ≥ 30 to ≤ 50 ml/min to 0.78%/year in NVAF patients with CrCl >130 ml/min. As described above, the trend towards a decreasing efficacy with edoxaban in patients with NVAF was relative to well managed warfarin, where the hazard ratio for edoxaban vs warfarin showed a rising trend as the creatinine clearance rose. Importantly, this trend was not statistically significant. Table 5 showed that the 95% confidence intervals for the hazard ratio were increasingly wide as creatinine clearance increased, corresponding to fewer absolute numbers of patients experiencing ischaemic stroke/SEE in both edoxaban and warfarin groups.

Daiichi-Sankyo submitted that an exploratory sub-analysis of the ENGAGE AF-TIMI 48 study, looking at the impact of renal function on outcomes with edoxaban (Bohula *et al* 2016) had been published. This noted that the 'Thromboembolic and bleeding event rates were lowest in those with the highest CrCl in all 3 treatment arms (warfarin, [high dose edoxaban regimen] HDER, and [low dose edoxaban regimen] LDER)'. HDER was the licensed dosing regimen of edoxaban which was discussed in the materials at issue.

Daiichi-Sankyo submitted that Bohula *et al* stated: 'The primary net clinical outcome of [stroke/SEE], major bleeding, and all-cause death was more favourable for HDER compared with warfarin across the range of renal function subgroups (CrCl 30–50 mL/min; HR, 0.86; 95% CI, 0.75–0.98; CrCl >50–95 mL/min: HR, 0.91; 95% CI, 0.82–1.00; CrCl >95 mL/min: HR, 0.93; 95% CI, 0.77–1.13; P for interaction=0.73... On the basis of a **nonsignificant interaction across renal subgroups**, findings were consistent with the overall trials results in which HDER was more favourable to warfarin for the secondary net clinical outcome of disabling stroke, life-threatening bleeding, or death (P for interaction=0.19) and tertiary exploratory net clinical end points comprising severe or irreversible events. However, **nonsignificant numerically higher rates** were observed with HDER versus warfarin in those with a CrCl >95 mL/min for these secondary and tertiary net clinical end points' (emphasis added).

Bohula *et al* went on to state 'exploratory analyses in patients with a CrCl >95 mL/min suggested lower **relative** efficacy for the prevention of thromboembolic events with HDER compared with warfarin. As a result of persistently lower rates of major bleeding in patients with a CrCl >95 mL/min, **the primary net clinical outcome remained favourable for HDER compared with warfarin'** (emphasis added).

Daiichi-Sankyo submitted that here again it was made clear that any decrease in efficacy for edoxaban in NVAF patients with high creatinine clearance was found only when compared to warfarin, and this was not statistically significant. It was also important to note that in relation to overall patient safety, when efficacy and safety were analysed together in the primary net clinical outcome analysis (a composite of stroke, SEE, major bleeding and all-cause death), edoxaban was favourable compared to warfarin. Daiichi-Sankyo therefore did not agree that the omission of the warning at issue from the body of promotional materials posed a risk to patient safety and this was evidenced above by the clinical data.

Prescribing practice

Daiichi-Sankyo submitted that both efficacy **and** safety of a medicine were considered when prescribers were deciding on the suitability of a medicine for a particular patient. The overall benefit/risk ratio was taken into account. For overall patient safety, the net clinical outcome (which combined efficacy and safety measures) was a more relevant measure than efficacy alone. A careful evaluation of the risks and benefits of a medicine should always be undertaken by any prescriber. The high creatinine clearance statement in the edoxaban SPC did not alter this obligation on prescribers.

Daiichi-Sankyo submitted that in order to have an adequate knowledge of a patient's health when considering prescribing any anticoagulant for a patient with NVAF, a doctor would have undertaken a careful evaluation of the patient's thromboembolic and bleeding risk. The high creatinine clearance statement in the edoxaban SPC therefore **did not require that doctors should do anything additional to what they would already do when evaluating the risks and benefits of a medicine.** The presence or omission of the high creatinine clearance statement from the body of promotional materials did not impact on what a doctor would be required to do in any prescribing situation. The omission of the wording from the body of promotional materials did not pose a risk to patient safety.

Relationship of high creatinine clearance to renal impairment

Daiichi-Sankyo submitted that it was relevant to note that patients with high creatinine clearance did not have renal impairment. High creatinine clearance was not a disease process (unlike renal impairment), and therefore people with high creatinine clearance were not regarded in clinical practice as having any problems with their kidney function, or as being a part of a special population. A patient with high creatinine clearance would not be flagged as having an abnormal result in blood test reporting systems. Indeed, in Bohula *et al*, people with CrCl > 95ml/min were described as having normal renal function. The authors noted that the European Medicines Agency '…did not place any restrictions on the use of edoxaban in patients with normal renal function'.

Lixiana Initiation Information Guide

Daiichi-Sankyo noted that 'The Panel noted that the stated purpose of the booklet in question to help prescribers initiate Lixiana appropriately and considered that failure to include the special warning was misleading and did not encourage the rational use of the medicine. In the Panel's view it was not sufficient to rely on the prescribing information at the back of the guide to provide the warning

about **the use of Lixiana and the trend towards the decreasing efficacy in patients with NVAF and high creatinine clearance'** (emphasis added).

Daiichi-Sankyo submitted that it appeared that the Panel considered that the absolute rate of ischaemic stroke and SEE increased in patients with NVAF as the creatinine clearance increased and made a judgement on that basis. However, as described above, this was not so. The trend towards decreasing efficacy with increasing creatinine clearance in patients on edoxaban with NVAF, was only when compared to well-managed warfarin. The absolute rate of ischaemic stroke and SEE actually fell with edoxaban in NVAF patients as creatinine clearance rose. The net clinical outcome also remained favourable for edoxaban compared to warfarin in NVAF patients as creatinine clearance rose.

Daiichi-Sankyo submitted that the Panel had also emphasised in its ruling the fact that there were sections in the material related to renal impairment and edoxaban dose modification. It appeared that the Panel considered that if there was discussion of renal impairment, there should also be discussion of high creatinine clearance. However, Daiichi-Sankyo disagreed that this should be the case. As described above, renal impairment was due to a disease process, whereas high creatinine clearance was not. Patients with high creatinine clearance had normal renal function. Therefore, discussion of high creatinine clearance would not logically fit into sections discussing renal impairment. The edoxaban SPC mandated reduction of the edoxaban dose in patients with renal impairment, which was why it was important that this was emphasised in all materials, to ensure patients were not over-dosed. However, there was no change of edoxaban dose recommended for patients with high creatinine clearance, which was why this was not given the same level of emphasis. The high creatinine clearance statement was instead given in the prescribing information. The reader was referred on page 1 of the material to the SPC for full prescribing information. The recommendations given in the body of the material were entirely consistent with the SPC and the material was not misleading, and therefore not in breach of Clause 7.2.

Daiichi-Sankyo noted that as discussed above, in carrying out their prescribing duties, doctors were expected to have an adequate knowledge of a patient's health, which would include a careful evaluation of their thromboembolic and bleeding risk. There was nothing in the material that recommended that doctors should not carry out their usual obligations to assess a patient's health before prescribing edoxaban or recommended use of edoxaban in a manner that was not rational, and therefore the material was not in breach of Clause 7.10.

Consequently, high standards had been maintained, and Daiichi-Sankyo did not agree that omitting the wording was a risk to patient safety. Therefore, Daiichi-Sankyo submitted that this material was not in breach of Clauses 9.1 or 2.

Lixiana Practical Guide

Daiichi-Sankyo noted the Panel's view that the '... failure to include the special warning at issue, particularly considering there was a page dedicated to special patient populations was misleading and did not encourage the rational use of a medicine'.

Daiichi-Sankyo submitted that directly below the Special Patient Populations heading on page 15 the Practical Guide stated 'Several groups of patients are at increased risk of bleeding and should be carefully monitored for signs and symptoms of bleeding complications'. It was clear to the reader that this page was specifically talking about special patient populations at increased risk of bleeding. The material also contained sections on 'Patients at Potentially Higher Risk of Bleeding', and 'Management of Bleeding Complications'. Bleeding was the primary safety concern when considering the use of any anticoagulant, as it could have devastating consequences for a patient, which was why this particular topic was strongly emphasised. Patients with high creatinine clearance **were not at increased risk of bleeding**, and therefore the statement from the edoxaban SPC regarding high creatinine clearance would not logically fit into these sections. Furthermore, these patients would not be regarded by doctors as being part of a special patient population, as they had normal renal function. Therefore, this material was not misleading or in breach of Clause 7.2.

Daiichi-Sankyo submitted that as above, in carrying out their prescribing duties, doctors were expected to have an adequate knowledge of a patient's health, which would include a careful evaluation of their thromboembolic and bleeding risk. There was nothing in the material that recommended that doctors should not carry out their usual obligations to assess a patient's health before prescribing edoxaban or recommend use of edoxaban in a manner that was not rational, and therefore the material was not in breach of Clause 7.10.

Consequently, Daiichi-Sankyo submitted that high standards had been maintained, and it did not agree that omitting the wording was a risk to patient safety. Therefore, Daiichi-Sankyo submitted that this material was not in breach of Clauses 9.1 or 2.

Summary

Daiichi-Sankyo submitted that the materials were not misleading in that the materials did encourage the rational use of edoxaban. Consequently, high standards had been maintained. Patient safety had not been put at risk and therefore Daiichi-Sankyo appealed the Panel's ruling of a breach of Clause 2 for the materials.

Daiichi-Sankyo submitted that as stated previously, all doctors were expected to have an adequate knowledge of a patient's health prior to any prescribing decision. Thromboembolic risk and bleeding risk were integral factors of an NVAF patient's health that a doctor would evaluate when considering the appropriate anticoagulant to prescribe, whether that was edoxaban or another

product (such as warfarin). There was no evidence that the omission of the high creatinine clearance statement from the body of promotional materials had led to patient harm or could potentially lead to patient harm. On this basis Daiichi-Sankyo did not agree with the Panel that the omission of the high creatinine clearance statement from the body of promotional materials had put patients' safety at risk. Therefore, Daiichi-Sankyo did not agree with the Panel that Daiichi-Sankyo had brought discredit upon, and reduced confidence in the pharmaceutical industry, in breach of Clause 2.

Daiichi-Sankyo submitted that patient safety was central to its work and this was reflected in promotional materials. The materials pointed to situations where the dosage of edoxaban should be modified in line with the SPC in order to ensure patients were not over-dosed and not put at unnecessary risk of bleeding. There was also a strong emphasis on communicating data on bleeding which was the main safety concern of edoxaban and indeed all anticoagulants.

COMMENTS ON THE APPEAL BY THE ALLIANCE

The Alliance stated that it was notable that in Daiichi-Sankyo's response to its initial complaint to the PMCPA, a principal part of its defence was that the information relating to the precautionary wording was indeed included in the materials as part of the prescribing information and that this was sufficient. Daiichi-Sankyo's case now appeared to have shifted to one based on a general assertion that the precautionary wording did not need to be included at all.

The Alliance alleged that the rationale provided by Daiichi-Sankyo for its appeal relating to the omission of precautionary wording about the use of edoxaban in patients with a high creatinine clearance was long and complex but it could be distilled into a number of core points which it addressed below.

1 Daiichi-Sankyo's submission that the Panel was wrong to review the Lixiana Initiation Information Guide

The Alliance stated that this assertion demonstrated a lack of understanding of both the letter and principles of both the Code and the PMCPA Constitution and Procedure. The intercompany dialogue clearly demonstrated that Daiichi-Sankyo did not accept that the content of this material was in breach of the Code and that it had reserved the right to use similar content in the future, continuing to omit the essential precautionary statement relating to the use of edoxaban in patients with high creatinine clearance and therefore continuing to expose patients to unnecessary risk.

The Alliance noted Daiichi-Sankyo specifically stated in its appeal that 'The item the [Initiation Information Guide] was not discussed during a face-to-face meeting between the Alliance and DSUK'. Daiichi-Sankyo stated that the Alliance stated on 5 January 2018 that it considered 'all other matters raised in previous correspondence but not discussed at this [face-to-face] meeting to have been resolved'. The Alliance referred to its minutes for this meeting. In paragraph 8 of this document, entitled 'Addition of high creatinine clearance warning & precaution statement as per SPC on all promotional materials', the minutes clearly stated the following:

> 'Alliance expressed the concerns that there have been multiple promotional materials including EDX/17/0087(1), EDX/16/0171, EDX/15/0091(4), EDX/17/0032(1), EDX/15/0088(4), EDX/15/0070(2) without a clear cautionary statement with regards to the edoxaban use in patients with high creatinine clearance as mentioned in edoxaban SPC section 4.4.'

Thus, the Alliance alleged that it was clear that this item was discussed during intercompany dialogue as a specific example of the ubiquitous omission of this important warning statement. The Alliance therefore did not understand why Daiichi-Sankyo would state that this item was not discussed during this meeting.

Furthermore, the Alliance referred to Daiichi-Sankyo's letter to the Alliance, 22 December 2017. The final sentence of a paragraph entitled 'Patients with high creatinine clearance' stated that:

> 'DSUK does not make any specific claims about patients with high creatinine clearance in its materials so does not believe there is any requirement to make further mention of the precaution statement from Section 4.4 of the SmPC, beyond that which is already mentioned in the Prescribing Information'.

The Alliance noted that Daiichi-Sankyo's appeal referred to the Alliance correspondence dated 5 January 2018. This was a letter concluding the intercompany dialogue and stating how the Alliance intended to proceed. In this letter, a paragraph entitled 'Patients with high creatinine clearance, stated:

> 'I note that DSUK continues to assert that omission of information relating to this precautionary statement from the body text of any edoxaban materials does not constitute a breach of the Code as this information is contained within the prescribing information. However, the Alliance continues to interpret this considered and ubiquitous omission to be a clear and serious breach of clauses 7.2, 7.10, 9.1 and 2 of the Code. Unfortunately, as we have been unable to resolve this matter through inter-company dialogue, we will now be placing this matter before the PMCPA for their consideration.'

Thus, the Alliance alleged that the Daiichi-Sankyo claim that the Alliance could have, in any way, considered this to be a satisfactory outcome for the intercompany dialogue relating to this item was disingenuous and not supported by the records. In these circumstances the Panel was clearly entitled to consider whether this material was in breach of the Code.

2 Daiichi-Sankyo's submission that the precautionary statement related only to edoxaban when compared to well-controlled

warfarin and not to the 'absolute efficacy of edoxaban when viewed in isolation'

The Alliance alleged that this assertion was difficult to comprehend as it appeared to be based on a complete misunderstanding of the role of controlled clinical trials in the investigation of a medicine's efficacy and safety, and the regulatory approval process. All the Non-Valvular Atrial Fibrillation pivotal regulatory trials for all the NOACs were conducted with warfarin as the comparator medicine. Therefore, all the efficacy and safety information relating to the NOACs, upon which the EMA licensing decisions were made and which was reflected in the wording of their SPCs, were derived from comparisons with warfarin. Similarly, an expressed concern of the regulatory authorities about decreased efficacy in patients with high creatinine clearance was derived from the comparative data. This issue was only highlighted in the edoxaban registration trials and not the other NOACs. Therefore, it was only the edoxaban SPC (and not the other NOAC SPCs) that contained the precautionary wording in patients with high creatinine clearance.

3 Daiichi-Sankyo appeared to be asserting that the available data did not support the precautionary statement

The Alliance noted that Daiichi-Sankyo had provided a detailed discussion of data derived from its pivotal ENGAGE study and its exploratory sub-analysis of these data. All of these data would have been made available to the regulatory authorities for consideration and would have been the basis of the decision by the EMA to include their precautionary wording about the use of this medicine, and by the FDA to contraindicate its use in this group of patients by the addition of a black box warning. It was not appropriate to attempt to undermine the decisions of the regulatory authorities simply because a company disagreed with their interpretation of its data. It was certainly not acceptable to simply ignore them for the same reason. Similarly, if there were new data or analyses which Daiichi-Sankyo considered could lead the regulatory authorities to change their opinion then it should submit them for appropriate regulatory consideration. Daiichi-Sankyo was not in a position to make decisions about the validity, or otherwise, of its SPC wording without the appropriate discussions with the regulatory authorities. The precautionary wording within the edoxaban SPC was clear and Daiichi-Sankyo had an obligation to ensure that all UK health professionals were properly informed about it when they were making their prescribing decision.

4 Daiichi-Sankyo stated that it was not necessary to include the precautionary wording in promotional material because it did not impact on what a doctor would be required to do in any prescribing situation

The Alliance alleged that when decisions were made about the clinical management of atrial fibrillation which might entail the use of anticoagulation there were usually two steps involved:

a) Is anticoagulation needed?
b) If so, which anticoagulant should be used?

The Alliance alleged that it was the second of these decisions which could be influenced by awareness of the precautionary wording under discussion here. Section 1.5 of the current NICE guidance on the management of atrial fibrillation (Clinical guideline [CG180] Published June 2014 Last updated: August 2014) stated the following:

> 'Discuss the options for anticoagulation with the person and base the choice on their clinical features and preferences.'

Section 1.2 of the NICE Technology Appraisal: Edoxaban for preventing stroke and systemic embolism in people with non-valvular atrial fibrillation, Technology appraisal guidance [TA355] Published, 23 September 2015, stated the following:

> 'The decision about whether to start treatment with edoxaban should be made after an informed discussion between the clinician and the person about the risks and benefits of edoxaban compared with warfarin, apixaban, dabigatran etexilate and rivaroxaban. For people considering switching from warfarin, edoxaban's potential benefits should be considered against its potential risks, taking into account the person's level of international normalised ratio (INR) control.'

The Alliance alleged that there was now a choice for clinicians and patients when it came to choosing which oral anticoagulant to select for the prevention of stroke and systemic embolism in non-valvular AF. There were four NOACs and vitamin K antagonists. The clinical profiles of patients differed, as did the profiles and characteristics of the available oral anticoagulants. This was acknowledged and encompassed in the NICE recommendations quoted above. In order for the discussions and decisions recommended by NICE to take place, both clinicians and patients must be fully informed about the risks and benefits of all the options. The precautionary wording regarding high creatinine clearance was unique to edoxaban and both clinicians and patients were entitled to be made fully aware of it.

5 Daiichi-Sankyo stated that high creatinine clearance was not a disease state and also appeared to consider that therefore these patients were not at-risk and were also therefore not worthy of inclusion as a special patient population in their promotional material.

The Alliance alleged that the fact that a particular patient characteristic was not a disease state did not preclude its inclusion in an SPC as requiring precautionary wording. Pregnancy, low weight and advanced age were examples of special populations that were not disease states but required special attention to minimise risk. Similarly, patients with high creatinine clearance were a special population that the regulators had identified as requiring special attention to minimise risk if edoxaban was being considered. Indeed, the precaution was not a dosing modification but a determination as to whether to

use edoxaban at all in this population based on a benefit-risk evaluation. Bleeding was indeed an important risk for consideration when prescribing anticoagulants and it was true that patients particularly at risk from such bleeding were a special population. However, they were not the only special patient population and they were not the only population at risk. To state that a particular patient group was excluded from a risk discussion because they did not fit the description of the headings Daiichi-Sankyo had chosen to include in, or exclude from, its own material appeared an unconvincing explanation.

Daiichi-Sankyo actually stated in its appeal that these patients would not be regarded by doctors as being part of a special population, as they had normal renal function. The Alliance alleged that the consequences of lack of efficacy could be every bit as serious as those of bleeding. The purpose of the precautionary wording was to reduce the risk that patients with high creatinine clearance might experience a reduction in efficacy on edoxaban and as a consequence be at increased risk of stroke, disability and even death. It was uncommon to have such strong precautionary wording for patients with high creatinine clearance and it would be usual for clinicians to assume that, in the absence of any information to the contrary, patients with what they considered to be normal renal function would not be at any increased risk. If doctors were unaware that these patients should perhaps be on another anticoagulant other than edoxaban, because they did not consider them to be at risk, then surely this was the strongest reason possible why they needed to be made aware of the precautionary wording. It was worth remembering that mention of the precautionary wording relating to this at-risk special patient population was omitted from every single piece of promotional material, both electronic and hard copy, used by Daiichi-Sankyo to promote edoxaban in the UK. As the Alliance indicated, the NHS had been adopting guidelines relating to the use of edoxaban and these commonly did not make any reference to this warning and precaution in patients with high creatinine clearance. This suggested there was widespread failure by Daiichi-Sankyo to inform prescribers and payors of this warning and precaution. This comprehensive omission of important information from all promotional material was potentially putting at risk a significant proportion of patients who were receiving, or might be prescribed, edoxaban. Hence the request by the Alliance that Daiichi-Sankyo take immediate action to withdraw these promotional materials, and urgently inform the healthcare community of this important warning. Recent evidence suggested up to 15% of patients with AF had high creatinine clearance, illustrating the magnitude of this potential patient safety issue.

6 Daiichi-Sankyo's submission that there was no evidence that the omission of the precautionary statement from the body of its promotional materials had led to patient harm or could potentially lead to patient harm

The Alliance stated that the enforcement of compliance with the Code was designed to prevent anyone coming to harm as a result of non-compliance. It was not a requirement that, before a breach could be judged, it must be demonstrated that the breach had actually resulted in harm to patients or the general public. Similarly, the wording of any medicine's licence was based on a review of all the clinical and preclinical data by the regulatory authority and was designed to ensure that the potential risks to a patient from use of the medicine were minimised whilst at the same time increasing the chances that the patient would obtain benefit. Daiichi-Sankyo might consider that there was no evidence that concealing the important precautionary wording from prescribers could potentially lead to patient harm but by their inclusion of this wording in the edoxaban SPC and label information, uniquely for this medicine within the NOAC class, both the EMA and the FDA had demonstrated that their review of the evidence had led them to a different conclusion.

In summary:

- The PMCPA was entitled to review all the materials currently under discussion
- The precautionary wording was a general warning about the potential for decreased efficacy of edoxaban in a specific population. Daiichi-Sankyo's use of terms such as 'absolute efficacy' or efficacy 'viewed in isolation' was meaningless in the context of SPC recommendations based on controlled clinical trials.
- The precautionary SPC wording in patients with high creatinine clearance was the result of an in-depth consideration of all the available data by the regulatory authorities. Daiichi-Sankyo had a responsibility to make it clear in its promotional material that these patients required particular consideration. The fact that Daiichi-Sankyo disagreed with the regulatory authority's interpretation of these data did not give it the right to pretend that this precautionary wording did not exist. Similarly, if Daiichi-Sankyo had new data or analyses which it thought might change the situation then it should discuss it with the regulatory authorities and not try and use it as a defence for its disregard of the requirements of the Code.
- The Alliance alleged that clinicians and patients with non-valvular AF now had a choice about which anticoagulant they wished to use. NICE recommended an informed discussion to decide amongst all the different options. All the available options had different profiles. These differences, positive and negative, should be transparently available to clinicians to enable them to have an intelligent, informed discussion with their patients. The precautionary wording relating to patients with high creatinine clearance was unique to edoxaban and was therefore potentially an important consideration for these prescribing decisions. The ubiquitous omission of any mention of this precaution from any Daiichi-Sankyo promotional material was a serious breach of the Code which had the potential to put a significant proportion of patients with non-valvular AF at risk of stroke, disability or death.
- High creatinine clearance, whilst not a disease state, might have a potential for increased risk

in such patients (a significant proportion of all patients with non-valvular AF) if edoxaban was used. These patients therefore should be considered as a special patient population. Excluding them from promotional material merely because they did not fall into the categories of risk which Daiichi-Sankyo had chosen (principally renal disease and bleeding) was highly misleading, and potentially impacted the safety of patients.

- It was not necessary to demonstrate that any patient had suffered harm before a breach of the Code could be ruled. Furthermore, it was the opinion of the regulatory authorities that there was sufficient evidence of a potential for a reduction in efficacy with edoxaban in patients with a raised creatinine clearance, hence the precautionary wording, which therefore also needed to be included in promotional material. The contrary opinion of Daiichi-Sankyo regarding the lack of evidence of potential for patient harm was irrelevant.

After receipt of the outcome in this case and prior to being notified of Daiichi-Sankyo's appeal the Alliance requested, *inter alia*, that Daiichi-Sankyo suspend use of the material at issue pending the outcome of any appeal. The Alliance provided three guidance documents from the NHS on the use of direct oral anticoagulants (DOACs) in NVAF where there was quite detailed information on prescribing more medicines where there was no reference to the consideration for high creatinine clearance with edoxaban. The Alliance separately requested that due to potential safety issues that Daiichi-Sankyo be required to take reparative action.

The Alliance's view was that Daiichi-Sankyo should be required to proactively communicate to all relevant UK prescribers and other relevant decision makers to include those NHS organisations which had issued guidance on the use of edoxaban in NVAF. The Alliance also provided data which showed that the proportion of patients with good renal function eligible for treatment with edoxaban was in the order of 14%. Daiichi-Sankyo proposed in its NICE submission that the proportion was 5-10%.

The Alliance's submission was provided to Daiichi-Sankyo for comment and in response it stated, *inter alia*, that that the Lixiana Initiation Information Guide was withdrawn prior to intercompany dialogue and that the Lixiana Practical Guide was recalled on 20 August due to an update to the prescribing information. Daiichi-Sankyo submitted that it had suspended use all Lixiana promotional materials pending the outcome of the appeal.

APPEAL BOARD RULING

The Appeal Board noted the warning about decreased efficacy in patients with high creatinine clearance in the Lixiana SPC. Section 4.4 of the Lixiana SPC, Special warnings and precautions for use, stated under the sub heading, Renal function in NVAF:

> 'A trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin (see section 5.1). Therefore, edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful evaluation of the individual thromboembolic and bleeding risk.
>
> Assessment of renal function: CrCL should be monitored at the beginning of the treatment in all patients and afterwards when clinically indicated (see section 4.2).'

The Appeal Board noted that the warning referred to a 'trend towards decreasing efficacy'. It also noted the comments in the NICE guidance about the size of the patient population with good renal function (measured by creatinine clearance) who would be eligible for treatment with edoxaban was in the region of 5-10%. The Appeal Board also noted the data submitted by the Alliance in this regard.

The Appeal Board noted that the FDA had contraindicated the use of Lixiana in this group of patients and noted Daiichi-Sankyo's submission that the EMA had assessed the data differently. Nevertheless, there was a warning about use in a patient population with normal kidney function which the Appeal Board considered was unusual. Both items at issue referred readers to the SPC for full prescribing information. In answer to a question at the appeal, the Daiichi-Sankyo representatives referred to an ongoing relevant study, the results of which were not yet available.

The Appeal Board noted that the Lixiana 'Initiation Information Guide' was a 6 page booklet containing important summary information designed to help prescribers initiate Lixiana appropriately including under the following headings: switching, contraindications, cautions, pregnancy and breast feeding, hepatic impairment, renal impairment and monitoring. There was no reference in the body of the booklet to the SPC warning at issue. The Appeal Board considered that prescribers would not necessarily expect patients with high creatinine clearance and thus normal kidney function to be at risk when prescribing a NOAC for NVAF; it was counter intuitive. It was therefore even more important that the SPC warning in question was drawn to their attention, particularly as Lixiana was the only NOAC that had this specific warning. The Appeal Board considered that it was wholly inadequate for Daiichi-Sankyo to only rely on the inclusion of the warning at issue in the prescribing information. Material had to be capable of standing alone with regard to the requirements of the Code and could not rely on qualification in either the prescribing information or a footnote. Other warnings from the SPC were included in the main body of the Initiation Information Guide, including in the Appeal Board's view special warnings and precautions with less strong wording and to omit the warning at issue downplayed its relative importance. The Appeal Board noted the position with the FDA. The Appeal Board considered that given the nature of the warning it was paramount that it appeared prominently in the body of the item at issue.

The Appeal Board thought it odd that, according to the company representatives, its field force had been trained on the warning at issue yet the company had omitted the warning from the body of the materials.

The Appeal Board considered that the failure to include the special warning in the body of the Initiation Information Guide was misleading and did not encourage the rational use of the medicine. The Appeal Board noted the Alliance's submission about the potential life-changing or even fatal consequences of failing to undertake such an evaluation in the relevant patient population. The Appeal Board upheld the Panel's rulings of a breach of Clauses 7.2 and 7.10. The Appeal Board considered that Daiichi-Sankyo had failed to maintain high standards and it upheld the Panel's ruling of a breach of Clause 9.1. The appeal on these points was unsuccessful.

The Appeal Board noted that the Lixiana Practical Guide was a 19 page booklet for prescribers. It included information on, *inter alia*, indications, summary of efficacy and safety, dosing recommendations, dose reductions, populations at potentially higher risk of bleeding, and special patient populations.

The Appeal Board considered that comments above applied equally to this item. The Appeal Board noted that the Practical Guide covered more matters than the Initiation Information Guide and included discussion of efficacy and safety issues including patients at higher risk of bleeding and special patient populations. The Appeal Board considered that the failure to include the special warning at issue in the body of the item, particularly considering there was a page dedicated to special patient populations and the missing information appeared in SPC under the heading special populations, was misleading and did not encourage the rational use of the medicine. The Appeal Board upheld the Panel's rulings of a breach of Clauses 7.2 and 7.10. The Appeal Board considered that Daiichi-Sankyo had failed to maintain high standards and it upheld the Panel's rulings of a breach of Clause 9.1. The appeal on these points was unsuccessful.

The Appeal Board noted the comments in the NICE guidance about the size of the patient population with good renal function. The Appeal Board further noted the trend towards decreasing efficacy of edoxaban with increasing creatinine clearance and the consequences of such and considered that Daiichi-Sankyo's failure to include the warning meant that it had potentially put those patients' safety at risk. Daiichi-Sankyo had not submitted any adequate explanation for this omission and it appeared had not treated patient safety as a priority. The Appeal Board considered that patient safety was of the utmost importance and Daiichi-Sankyo's failure in this regard brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board upheld the Panel's ruling of a breach of Clause 2 in relation to each item. The appeal on this point was unsuccessful.

The Appeal Board noted its comments and rulings of breaches of the Code in the above including a breach of Clause 2. The Appeal Board considered that Daiichi-Sankyo's actions had meant that prescribers had been provided with material that failed to highlight an important patient safety consideration and consequently patients might have been put at risk. This was totally unacceptable. The Appeal Board noted that the NHS guidance on the use of DOACs in NVAF provided by the Alliance made no reference to the warning at issue. Consequently, the Appeal Board decided, in accordance with Paragraph 10.6 of the Constitution and Procedure, to require Daiichi-Sankyo to issue a hard copy corrective statement to all recipients of the material at issue. In addition, the Appeal Board considered that given the items broad dissemination including that in the Appeal Board's view it was more likely than not that this material would have been shared by prescribers with colleagues, the Appeal Board considered that the corrective statement should also be sent to relevant UK prescribers. The corrective statement should refer to the case report. Under Paragraph 10.6 details of the proposed content and mode and timing of dissemination of the corrective statement must be provided to the Appeal Board for approval prior to use.

In addition, the Appeal Board decided, in accordance with Paragraph 10.3, to require Daiichi-Sankyo to take steps to recover the material from those who had received it; written details of the action taken must be provided to the Appeal Board. This should be included in the corrective statement.

2 – TWITTER

COMPLAINT

The Alliance was concerned about the use of the Twitter campaign by Daiichi-Sankyo and its agencies to promote Lixiana which used the hashtag '#safeplicity' - clearly derived from combining the words 'safe' or 'safety' and 'simplicity'. In this regard, the Alliance noted that Clause 7.9 prohibited use of the word 'safe' without qualification. This prohibition applied equally to 'grammatical derivatives of the word such as 'safety'. (The Alliance also noted Article 3, Section 3.07 of the EFPIA Health Professional Code stated that 'The word "safe" must never be used to describe a medicinal product without proper qualification').

The Alliance noted that it was an established principle under the Code that companies were responsible under the Code for external persons or groups acting on their behalf or with their authority including advertising agencies, PR agencies and meeting organisers. If a breach of the Code occurred in relation to an activity carried out on a pharmaceutical company's behalf, then that company would be held responsible.

The Alliance noted particular Twitter posts (copies provided) which could be found on Twitter at #safeplicity. It was clear from these posts that:

1 The #safeplicity had been used to promote Lixiana. In the screenshots provided of the Twitter feed, there were a number of posts which consisted of photographs which prominently

included both the hashtag claim '#safeplicity' and the brand name and branding colours of Lixiana. A number of these had apparently been posted by employees of the UK agency engaged by Daiichi-Sankyo to develop its congress stand and promotional activities. During inter-company dialogue, Daiichi-Sankyo UK had stated that its parent company, Daiichi-Sankyo Europe GmbH based in Germany, had used this hashtag and instructed UK-based agencies to use it as well. The hashtag was also used frequently on the Twitter feed for Daiichi-Sankyo Europe and when readers clicked on this hashtag they were transferred to the hashtag page which contained promotional photographs. However, it was not made clear in any of the posts by these agencies that the activity was sponsored by Daiichi-Sankyo. Neither was it clear from the Daiichi-Sankyo posts that by clicking on the #safeplicity readers would access Lixiana promotional material. This constituted disguised promotion. Furthermore, as Twitter was very widely used by the public, this promotional activity was also accessible by the public.

2 This promotion was carried out by Daiichi-Sankyo and its UK based agencies. The term safeplicity and the #safeplicity were developed by these agencies and therefore originated in the UK. (The Alliance referred to the highlighted sections of the screenshots provided of these agencies showing their location and that the scope of their work for Lixiana was promotional).

3 Since the Alliance initiated inter-company dialogue with Daiichi-Sankyo on the matter, this hashtag had continued to be used on Twitter, including on the Daiichi-Sankyo Europe twitter feed – the latest example of which was 29 December 2017.

During inter-company dialogue The Alliance had asked Daiichi-Sankyo to immediately stop using the #safeplicity or the term safeplicity in any of its materials or activities and remove it from any search engine optimisation systems in which it might have been included.

The Alliance also asked Daiichi-Sankyo to explain in detail what it proposed to do to ensure no further use of this term or hashtag. Daiichi-Sankyo UK, however, had stated that it was unable to give any undertakings about the further or continued use of the hashtag. Daiichi-Sankyo had stated that its parent company, Daiichi-Sankyo Europe GmbH based in Germany, had, however, used this hashtag and instructed UK agencies to use this hashtag. The hashtag was displayed at the Daiichi-Sankyo Europe stand at the European Society of Cardiology (ESC) congress 2017 in Barcelona, and UK health professionals were sponsored by Daiichi-Sankyo UK to attend the ESC. Daiichi-Sankyo UK was asked during the inter-company dialogue whether any Daiichi-Sankyo UK personnel manned this stand but was unable to provide that information. Daiichi-Sankyo UK had apparently informed Daiichi-Sankyo Europe GmbH of its strong concerns regarding the appropriateness of this hashtag and advised that it was no longer used. However, the hashtag continued to be used. Daiichi-Sankyo UK had asserted that as it was not involved with the commissioning of this hashtag, and did not encourage health professionals, patients or the public to view any messages containing this hashtag, it did not believe this fell within the scope of the Code.

The Alliance's view was that this was a very serious matter. The promotional use of the term safeplicity and the hashtag on Twitter, originating in the UK, was in breach of both the ABPI and EFPIA Codes. In the Alliance's view, this activity brought the pharmaceutical industry into disrepute and therefore needed to be stopped immediately. The Alliance alleged breaches of Clauses 7.9, 12.1, 26.1, 26.2, 9.1 and 2.

RESPONSE

Daiichi-Sankyo UK stated that it had never and did not intend to use the #safeplicity or any term similar to 'safeplicity' in any materials or activities targeted at UK health professionals or members of the public; it had not commissioned any external party (UK based or otherwise) to use the #safeplicity or 'safeplicity' as a term.

Daiichi-Sankyo noted that its parent company, Daiichi-Sankyo Europe GmbH was based in Germany. The Twitter posts submitted by the Alliance showed pictures of Daiichi-Sankyo Europe's stand at the ESC congress in Barcelona. Daiichi-Sankyo Europe was responsible for the set-up and design of the stand. Daiichi-Sankyo UK had no input into the design. Daiichi-Sankyo UK did not send any tweets or commission any external party to send any tweets regarding the ESC congress. An agency was commissioned directly by Daiichi-Sankyo Europe to develop the #safeplicity concept. Another agency was commissioned directly by Daiichi-Sankyo Europe to design the stand at ESC which displayed the #safeplicity wording. Although both agencies had offices in the UK, they were not contracted by and had not acted on behalf of Daiichi-Sankyo UK, and the #safeplicity messaging and ESC activities took place outside the UK.

During the course of inter-company dialogue the Alliance had alleged that another agency also had a role in the use of #safeplicity. Due to a lack of relevant contract information from Daiichi-Sankyo Europe available to Daiichi-Sankyo UK at the time, this allegation was not then contested or disputed by Daiichi-Sankyo UK. Having now received the correct information, Daiichi-Sankyo confirmed that neither Daiichi-Sankyo UK nor Daiichi-Sankyo Europe had commissioned this agency to use the term 'safeplicity' in any form. Indeed, Daiichi-Sankyo could find no evidence on Twitter that the agency had used this hashtag. The Alliance had not provided evidence to show that the agency had used this hashtag and it was unclear why the Alliance initially thought that the agency was involved with the #safeplicity concept.

The Alliance had asked Daiichi-Sankyo UK to remove the term 'safeplicity' from search engine optimisation systems. Daiichi-Sankyo UK had not

carried this out and had no knowledge of any search engine optimisation activities relating to the term 'safeplicity'. The Lixiana.co.uk website had never contained any metadata which would link an internet search for 'safeplicity' to the UK site.

Daiichi-Sankyo UK sponsored UK health professionals to attend the ESC in Barcelona in August 2017. The Daiichi-Sankyo Europe stand was in an area of the congress venue clearly demarcated for promotional stands from various companies. The UK health professionals were never briefed or invited by Daiichi-Sankyo UK or Daiichi-Sankyo Europe to attend the Daiichi-Sankyo Europe promotional stand.

At the time of a meeting between Daiichi-Sankyo UK and the Alliance, Daiichi-Sankyo UK did not have details to hand of any Daiichi-Sankyo UK staff who had worked on the ESC stand and was unable to answer the Alliance's question in this regard. Two UK representatives worked on the stand but they were not briefed to specifically target UK health professionals. The two staff members received stand briefings directly organised by Daiichi-Sankyo Europe in Barcelona prior to the start of the ESC. Daiichi-Sankyo UK did not have previous sight of the briefing presentation. Daiichi-Sankyo provided the full briefing deck (ESC 2017 – Booth Staff Training), although as explained below, neither representative saw the full deck.

Daiichi-Sankyo stated that one of the representatives was an hour late for the main briefing session, the day before ESC started, so did not see the beginning of the deck. According to the agenda timings on slide 8 of the deck, the representative would have seen from slide 65 onwards. This was consistent with the representative's recollection of the briefing given below.

The representative logged interactions with two UK health professionals during ESC on Daiichi-Sankyo UK's contact recording system. According to the statement provided by the representative below, those interactions did not take place on the Daiichi-Sankyo Europe stand. The representative confirmed that Daiichi-Sankyo UK told him/her that the ABPI Code must apply in all interactions with health professionals.

The statement provided by the representative was:

> 'Just to confirm that my time allocated manning the stand at ESC I did not see any UK customers, customers recorded in … were from interaction in the evening or off of the Daiichi stand.
>
> I attended part of the briefing meeting, where logistics around how the stand was built and the different zone areas of the stand were discussed, this was an opportunity to get to know my colleagues and to discuss good practice when manning a stand i.e. not eating on stand, not talking or texting on phone etc. At no time was clinical data discussed.
>
> Marketing from the UK had already briefed the UK team that this is a different environment from the UK around various messages that other countries may use myself and my UK colleagues were always to follow UK ABPI rules in any interaction with customers.'

The other representative also did not attend the main briefing session as he/she arrived in Barcelona on the opening morning of the ESC, and so had a shortened briefing. The Daiichi-Sankyo Europe trainer had stated:

> 'I did not create a bespoke presentation for the catch-up briefing the next day. I used the same deck but obviously focused on the main booth expectation points from the main briefing from the previous day. I'm confident that the focus was on logistics and rota management rather than safeplicity or other marketing messages simply because of the time limitation.'

The other representative logged interactions with six UK health professionals during ESC. According to a statement provided by him/her, those interactions did not take place on the Daiichi-Sankyo Europe stand. The representative also confirmed that Daiichi-Sankyo UK told him/her that the ABPI Code must apply in all his/her interactions with health professionals.

The statement provided by the second representative was:

> 'Contacts recorded in … were based on conversations at evening meetings on the days of the conference.
>
> … [Daiichi-Sankyo UK Marketing] told me to adhere to the UK code, which superseded any other guidance.
>
> The briefing I attended on the Saturday was not the full briefing held the previous day. The key messages I recall were ensuring we used only authorised ipads and all additional enquiries were directed to the medical team.'

Although two UK staff worked on the Daiichi-Sankyo Europe stand, there was no evidence that they interacted with UK health professionals on the stand, and they both recalled being instructed by Daiichi-Sankyo UK to follow the ABPI Code, regardless of any briefing they received from Daiichi-Sankyo Europe.

UK health professionals were not specifically targeted either by Daiichi-Sankyo UK or Daiichi-Sankyo Europe to view the Daiichi-Sankyo Europe stand or to be exposed to any #safeplicity messaging which was on the stand.

Daiichi-Sankyo UK had made very clear to Daiichi-Sankyo Europe that it was very concerned about the use of the term 'safeplicity' or the associated hashtag in any scenario. It was certainly not a term Daiichi-Sankyo UK intended to use in the UK. However, Daiichi-Sankyo could not give an undertaking that Daiichi-Sankyo Europe would not continue to use this term in promotional campaigns on the internet or at European congress stands outside the UK. Daiichi-Sankyo stressed, however, that UK health

professionals and members of the public were not specifically targeted by this campaign.

Daiichi-Sankyo UK stated it had not commissioned any party to use the #safeplicity. Furthermore, no Daiichi-Sankyo affiliate had specifically targeted UK health professionals, other relevant decision makers or members of the public with messaging containing this hashtag or similar terminology. Therefore Daiichi-Sankyo denied a breach of Clause 7.9.

Daiichi-Sankyo UK stated it had had no involvement in the use of the #safeplicity on the internet and UK health professionals had not been specifically targeted. Any promotion that occurred on the Daiichi-Sankyo Europe stand at ESC 2017 was organised by Daiichi-Sankyo Europe, not Daiichi-Sankyo UK, and was in an area clearly demarcated for promotion. Daiichi-Sankyo therefore denied that there had been any disguised promotion or any breach of Clause 12.1.

Daiichi-Sankyo UK stated it had had no involvement in the use of the #safeplicity on the internet, there had been no advertising of medicines to the public by Daiichi-Sankyo UK, so it denied any breach of Clause 26.1. Daiichi-Sankyo denied that unfounded hopes of successful treatment had been raised, or that any misleading statements had been made about the safety of medicines. Daiichi-Sankyo therefore denied a breach of Clause 26.2.

Further to the above, Daiichi-Sankyo did not believe that high standards had not been maintained, or that Daiichi-Sankyo UK had brought discredit to, or reduced confidence in, the pharmaceutical industry. Therefore, Daiichi-Sankyo denied breaches of Clauses 9.1 and 2.

In response to a request for further information Daiichi-Sankyo submitted that a master services agreement with one of the agencies was signed in 2014 was in place at the time of ESC 2017, although the agreement did not specifically mention ESC 2017. This agency carried out work related to ESC 2017 as well as other projects as part of the master services agreement.

According to Daiichi-Sankyo briefings between Daiichi-Sankyo Europe and the agency were conducted verbally through teleconferences and meetings, as part of the master services agreement. There were no written arrangements in place between Daiichi-Sankyo Europe and the agency that specifically related to ESC 2017 or #safeplicity. The agency was verbally briefed on the use of the #safeplicity during these meetings and designed the ESC stand according.

Daiichi-Sankyo Europe's social media policy and social media procedure applied in the UK; the UK did not have a separate policy in that regard.

Daiichi-Sankyo submitted that Daiichi-Sankyo Europe wrote 25 tweets relating to ESC 2017 from its Twitter account @EUdaiichisankyo in the lead up to and during ESC 2017. Only four members of staff were able to write tweets from this account, all worked in corporate communications and were subject to Daiichi-Sankyo Europe's social media policy and social media procedure. At the time of ESC 2017, the Twitter account @EUdaiichisankyo had 5519 followers. Daiichi-Sankyo submitted that it was not possible to obtain information on the nationality of the followers as this information was not available, they might be individuals or organisations. Daiichi-Sankyo submitted that there was no specific intended audience for the Daiichi-Sankyo Europe Twitter feed. The wording associated with the account, which was visible to all visitors to the page was: 'This channel is provided by the pharmaceutical company Daiichi-Sankyo Europe GmbH' which was followed by a link to the community guidelines. Daiichi-Sankyo submitted that there was no intended specific audience for the agency's Twitter feed. The wording associated with the account, which was visible to all visitors to the page was: 'Award winning strategy, design and management for conferences, exhibitions and events'.

Daiichi-Sankyo submitted that whilst an account had been created (@DaiichiSankyoUK), this had only been to reserve the username and ensure nobody else could use it. The account was protected and the profile was not accessible to the public. The only tweet ever sent from the account was for testing purposes and was not visible to the public. There was no intention that this account would ever be used to disseminate any information.

The UK health professionals sponsored by Daiichi-Sankyo UK to attend ESC 2017 received an invitation from Daiichi-Sankyo UK and subsequently a welcome letter from Daiichi-Sankyo Europe which referred to a 'welcome pack' to be picked up from the hotel. The welcome pack was the standard ESC pack available to all registered attendees plus the individual confirmation of registration and name badge. Daiichi-Sankyo did not have access to the materials in the welcome pack.

Daiichi-Sankyo submitted that the two UK account managers on stand duty spent 8.5 and 9 hours respectively manning the stand over the course of the congress.

Daiichi-Sankyo explained that the UK team had been briefed prior to ESC. As part of this briefing it was made clear that they must adhere 'to all UK SOPs and ABPI requirements'. After the UK team were briefed in Barcelona by Daiichi-Sankyo Europe, a named Daiichi-Sankyo UK employee verbally briefed them that they should 'adhere to the UK Code, which superceded any other guidance'.

PANEL RULING

The Panel noted that it could not make any rulings regarding the EFPIA Code as it had no locus to do so. National associations such as the ABPI were obliged as members of EFPIA to incorporate the requirements of the EFPIA Code into their local codes as far as national law permitted. The Panel noted that even if the UK Code did not apply Daiichi-Sankyo was an affiliate member of EFPIA.

The Panel noted that the complainant had provided twelve tweets, ten of which included the hashtags #ESCCongress, referring to the 2017 Congress in Barcelona, and #safeplicity and two of which included only #safeplicity. Two of the tweets were from employees of the agency, three were from another company and five were from Daiichi-Sankyo Europe (@EUdaiichisankyo). The Panel was unsure of the status of the senders of the remaining two tweets, they did not appear to be from Daiichi-Sankyo or from its employees or agents.

Firstly, the Panel had to decide whether the tweets in question were subject to the Code. The Panel noted that Clause 28.2 stated that information or promotional material about prescription only medicines which was placed on the Internet outside the UK would be regarded as coming within the scope of the Code if it was placed there by a UK company or an affiliate of a UK company or at the instigation or with the authority of such a company and it made specific reference to the availability or use of the medicine in the UK.

With regard to the tweets sent by Daiichi-Sankyo Europe, the Panel noted it was an established principle under the Code that UK companies were responsible for the acts or omissions of their overseas affiliates that came within the scope of the Code. Daiichi-Sankyo UK was thus responsible for any acts or omissions of Daiichi-Sankyo Europe and/or its agencies that came within the scope of the Code.

The Panel noted Daiichi-Sankyo UK's submission that the Twitter account in question belonged to Daiichi-Sankyo Europe based in Germany and the tweets' authors all worked in Daiichi-Sankyo Europe's corporate communications department. Daiichi-Sankyo UK further submitted that it had had no involvement in the use of the #safeplicity on the internet and that Daiichi-Sankyo UK did not send any tweets or commission any external party to send any tweets regarding the ESC congress. The Panel also noted Daiichi-Sankyo's submission that no affiliate had specifically targeted UK health professionals, other relevant decision makers or members of the public with messaging containing this hashtag or similar terminology. Daiichi-Sankyo was unable to provide information on the nationality of the followers of the Twitter account in question. The corporate tweets all contained the hashtag #safeplicity, one also contained the hashtag '#MakeYourHeartFeelGood' and another referred to avoiding heart problems during the holidays. The Panel was concerned about these tweets. The Panel noted that the tweets did not specifically refer to the use of medicines in the UK. The Panel noted that the UK company did not have its own active Twitter account and there was no evidence before the Panel that the UK company, its agents or affiliates, had directly or indirectly pointed UK health professionals or others to the Twitter account in question. The Panel thus considered that for all the reasons set out above the five tweets sent by Daiichi-Sankyo Europe were not within the scope of the Code and the Panel therefore ruled no breach of Clauses 7.9, 12.1, 26.1, 26.2, 9.1 and 2.

The Panel noted that the tweets would be covered by a code of practice and it was simply a question of which applied. As the tweets had been issued by Daiichi-Sankyo Europe based in Germany, the German Code might apply.

With regard to the tweets sent by employees at the agency, the Panel noted Daiichi-Sankyo's submission that the agency was a UK based agency commissioned directly by Daiichi-Sankyo Europe to design the stand at ESC, which displayed the #safeplicity wording. The safeplicity concept had been designed by another agency engaged by Daiichi-Sankyo Europe. The Panel noted that it was an established principle under the Code that pharmaceutical companies are responsible for work undertaken by third parties on their behalf which came within the scope of the Code. Thus, in the Panel's view if the agency's tweets came within the scope of the Code Daiichi-Sankyo Europe would be responsible for them and therefore the UK company would be responsible as it was responsible for its affiliates act/omissions which fell within the scope of the UK Code.

The Panel noted that Clause 28.1 stated that promotional material about prescription only medicines directed to a UK audience which was provided on the internet must comply with the Code. The Panel also noted the scope of the Code at Clause1.1 which covered promotional and certain non-promotional activities. The Panel considered that the tweets sent by the employees of a UK based agency were placed on the internet in the UK and published on a UK agency's Twitter account and were therefore within the scope of the Code.

The Panel considered that it was entirely foreseeable that a communications agency would use digital media to highlight its work with a pharmaceutical company. In the Panel's view it was good governance to discuss and agree such use at the outset. Daiichi-Sankyo Europe should have been aware that the agency in question had previously published photographs of its Lixiana stand at the 2016 ESC congress on its website and corporate Twitter account.

The Panel noted that one of the tweets dated 29 August was a picture of two of the agency's staff with the exhibition stand robot beneath the #safeplicity. The tweet included the hashtags #ESCCongress and #safeplicity, there was no direct reference to product. The second tweet was also dated 29 August but was sent by a different employee and featured a picture of a column which formed part of the exhibition stand and which bore the prominent #safeplicity above fire extinguishers. The author stated 'Oh how ironic' and in the left hand side of the photograph the brand name, Lixiana, in logo format was clearly visible. The tweet bore the hashtags safeplicity, esccongress and Barcelona. The Panel noted the Alliance's submission that the #safeplicity had been used to promote Lixiana and when readers clicked on this hashtag they were transferred to the hashtag page which it considered contained promotional photographs. Daiichi-Sankyo made no comment in this regard. The Panel considered that the hashtag

page was part of the complaint and noted that it contained references to Lixiana, including pictures of the exhibition stand robot which bore a screen which, on some tweets, clearly referred to Lixiana. Some tweets on the hashtag page referred to preventing stroke.

The Panel noted that the #safeplicity concept was commissioned by Daiichi-Sankyo Europe and in the Panel's view the content of the hashtag page which was linked to directly from the #safeplicity on the tweets in question was thus relevant when considering the acceptability of the tweets. In the Panel's view, the #safeplicity would generate open access social media activity in relation to Lixiana and the ESC and in this regard, was promotional. The Panel noted that Lixiana was a direct oral anticoagulant and considered that safeplicity was a strong unqualified claim. On one tweet, the Panel noted that the product name in logo format was clearly visible in the background of one photograph and its design and colour clearly linked it to the prominent safeplicity hashtag on the exhibition column in the foreground. The tweets had been published on the agency's open access Twitter accounts. Clicking on the #safeplicity took the reader to the safeplicity hashtag page described above which appeared to be, in part, a promotional vehicle for the product and where some tweets clearly referred to Lixiana. The Panel considered that the two tweets in question bearing the #safeplicity one of which referred to Lixiana and both linked to the hashtag page which referred to the product were promotional and promoted Lixiana to the general public. A breach of Clause 26.1 was ruled in relation to each tweet. These rulings were appealed.

The Panel considered that the hashtag safeplicity as used in the tweets in question and on the hashtag page would be clearly associated with Lixiana. The Panel noted that Clause 7.9 stated, *inter alia*, that the word 'safe' must not be used without qualification. The relevant supplementary information stated that these restrictions applied equally to all grammatical derivatives of the word safe such as safety. The Panel noted a slide from the Daiichi-Sankyo Europe's ESC 2017 briefing document stated 'How to summarize Lixiana in one single word? #safeplicity'. Below this it read 'Safety, efficacy and convenience of a once-daily NOAC for all of your NVAF and VTE patients'. In the Panel's view, the addition of 'plicity', which readers would associate with the word 'simplicity' to the word 'safe', compounded the already unacceptable impression given and implied that there was something straightforward or simple about the product's adverse event profile and, in the Panel's view, that was not so. The Panel noted the adverse effects of Lixiana as stated in Section 4.8 of the SPC and the special warnings and precautions for use in Section 4.4 of the SPC. The Panel considered that the term safeplicity used to describe Lixiana was inconsistent with the requirements of Clause 7.9 and a breach of that clause was ruled with regard to each of the agency's tweets. These rulings were appealed.

The Panel noted that Clause 26.2 stated that information about prescription only medicines available to the public, directly or indirectly must be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading about the safety of the product. The Panel noted its ruling of a breach of Clause 7.9 above and considered that the unqualified use of the term safeplicity was misleading about the safety of Lixiana. A breach of Clause 26.2 was ruled with regard to each of the agency's tweets. These rulings were appealed.

The Panel noted that Clause 12.1 stated that promotional material and activities must not be disguised. The supplementary information stated, *inter alia*, in addition that the identity of the responsible pharmaceutical company must be obvious. The Panel considered that this requirement was to ensure that promotional material was not disguised. The Panel considered that the tweets in question which linked to the hashtag page were, however, clearly promotional. No breach of Clause 12.1 was ruled.

The Panel considered that Daiichi-Sankyo had apparently been let down by its parent company. Nonetheless, noting the UK company's responsibility for its affiliate, the Panel noted its rulings above and considered that high standards had not been maintained in relation to the tweets in question. A breach of Clause 9.1 was ruled. The Panel noted that the supplementary information to Clause 2 gave prejudicing patient safety and/or public health as an example of activity likely to be in breach of the Code. Noting its comments and rulings above the Panel considered that Daiichi-Sankyo had brought discredit to and reduced confidence in the industry and ruled a breach of Clause 2. These rulings were appealed.

The Panel noted that the Alliance had referred to use of the hashtag by another UK agency. Daiichi-Sankyo submitted that neither it nor its European affiliate had commissioned the agency to use the hashtag in any form and could find no evidence that the agency had used the hashtag as alleged. The Panel noted that the Alliance bore the burden of proof and considered that it had not established that the hashtag had been used by that agency as alleged. No breach of Clauses 26.1, 26.2, 9.1, 7.2 and 2 were ruled.

The Panel noted that the Alliance had also provided tweets from another non-UK based agency which appeared to have created the robot used at the exhibition stand but made no specific allegations about that agency. Similarly, neither the complainant nor the respondent had identified the senders of the remaining two tweets, nor were specific allegations made about their content. Although the Alliance provided copies of these tweets, it had not made out its complaint including any UK link and the Panel therefore made no rulings in this regard.

The Panel then considered whether the use of the #safeplicity on the exhibition stand at the ESC 2017 Congress in Barcelona came within the scope of the Code. The Panel noted its comments above about the UK company's responsibility for the acts and omissions of its parent company that came within the scope of the Code.

Clause 1.1 stated that the Code applied to the promotion of medicines to members of the UK health professions and to other relevant decision makers. Furthermore, the supplementary information to Clause 1.1, Scope of the Code, stated that it also included 'promotion to UK health professionals and other relevant decision makers at international meetings held outside the UK, except that the promotional material distributed at such meetings will need to comply with local requirements'.

The Panel noted that the supplementary information to Clause 22.1, Meetings organised by Affiliates outside the UK, stated 'Companies should remind their affiliates outside the UK that the ABPI Code of Practice must be complied with if UK health professionals attend meetings which they organise regardless of whether such meetings occur in the UK or abroad'.

The Panel noted Daiichi-Sankyo UK's submission that it had sponsored UK health professionals to attend the ESC in Barcelona in August 2017 but these UK health professionals were not briefed or invited by Daiichi-Sankyo UK or Daiichi-Sankyo Europe to attend the Daiichi-Sankyo Europe promotional stand. The Panel noted Daiichi-Sankyo's submission that two UK employees manned the stand for 8.5 and 9 hours respectively over the course of the congress but were not specifically briefed to target UK health professionals. The Panel noted that one representative manning the stand logged interactions with two UK health professionals during ESC but these interactions did not take place at the Daiichi-Sankyo Europe stand. Similarly, the other representative logged interactions with six UK health professionals during ESC but also stated that these interactions did not take place on the Daiichi-Sankyo Europe stand. The Panel considered that although it was possible that a UK sponsored health professional attending the stand might prefer to speak to UK staff and/or might be directed towards UK staff there was no evidence before the Panel that this had occurred.

The Panel noted that the exhibition stand would be covered by a code, or codes it was a question of whether the UK Code applied. The Panel considered that there was no evidence to show that either Daiichi-Sankyo UK or Daiichi-Sankyo Europe had invited UK health professionals to visit the stand nor was there any evidence to show that Daiichi-Sankyo had any role in relation to the exhibition stand. On balance, the Panel thus did not consider that in the particular circumstances of this case the requirements of the UK Code applied and it ruled no breach of Clauses 2, 9.1,7.9, 26.1 and 26.2 of the Code because it considered that the matter of complaint did not fall within the scope of the Code.

During its consideration of this case the Panel was very concerned about the use of the #safeplicity and that the German affiliate had apparently continued to use it after the UK affiliate and the Alliance had raised concerns. The Panel noted its comments and rulings of a breach of Clauses 7.9 and 2 above.

The Panel was also very concerned at what it considered to be wholly inadequate training of UK staff manning the exhibition stand. The Panel noted Daiichi-Sankyo's response in this regard. Reminding staff that they had to be Code compliant was wholly insufficient given that UK staff were on an exhibition stand which bore the prominent #safeplicity. The exhibition stand, in the Panel's view, invited questions about safety and Lixiana and made an unqualified claim about the safety of the product. In the Panel's view, staff should have been trained on how to address such queries compliantly given the Panel's view above about the #safeplicity. The Panel was very concerned to note that the ESC 2017 booth staff briefing included extensive use of the words 'safety' and #safeplicity in relation to Lixiana. Whilst noting that such briefing to non-UK staff might not be within the scope of the UK Code the Panel queried whether such claims were consistent with the requirements of Clauses 7.9 and 2. Nonetheless, in the absence of any briefing to UK staff on how to respond to safety questions within the context of the stand the Panel was concerned that the stand environment including non-UK staff discussing safety as briefed and use of the #safeplicity on the stand might have influenced UK staff. There was no complaint in this regard.

The Panel queried whether it was likely that UK health professionals, particularly those invited to attend by the UK affiliate, would talk to neither of the UK representatives manning the stand particularly considering the length of time spent on the stand by each of them. Further, the Panel could not understand how the UK representatives could be expected to man the stand without referring to or being seen to use the promotional messages on it.

The Panel asked that Daiichi-Sankyo be advised of its concerns.

APPEAL BY DAIICHI-SANKYO

With regard to the use of #safeplicity, Daiichi-Sankyo UK submitted that it had never and would never make use of this hashtag or any similar messaging.

Daiichi-Sankyo understood the established principle that UK pharmaceutical companies were responsible for the acts and omissions of overseas affiliates that came within the scope of the Code. Daiichi-Sankyo understood that the agency was commissioned by Daiichi-Sankyo Europe and therefore acts and omissions by this agency which fell under the scope of the ABPI Code were also the responsibility of Daiichi-Sankyo UK. However, Daiichi-Sankyo did not believe that the agency's tweets fell under the scope of the ABPI Code for the reasons set out below.

Daiichi-Sankyo noted that Clause 28.1 stated that 'Promotional material about prescription only medicines **directed to a UK audience** which is provided on the Internet must comply with all relevant requirements of the Code' (emphasis added).

Daiichi-Sankyo noted that the Panel had considered that the two tweets sent by employees of the agency

were within the scope of the Code because it was a UK based agency, the tweets were placed on the internet in the UK and published on a UK agency's Twitter account. Daiichi-Sankyo did not agree with the Panel's assessment in this regard. There was no evidence that the agency's tweets were directed to a UK audience. In addition, there was no evidence that the tweets were placed on the internet in the UK. It was highly likely that the tweets were placed on the internet in Spain at the ESC 2017 conference.

Daiichi-Sankyo noted that Twitter was an international platform. The agency's Twitter page showed its location as 'Worldwide' and it described its business as 'strategy, design and management for conferences, exhibitions and events'. A screenshot of the Twitter page was provided and this indicated that it considered itself to be a worldwide events organisation and its activities spanned non-UK countries, as evidenced in this case where it operated at the ESC 2017 congress in Spain. There was no evidence and nothing within the tweets to suggest, that a UK Twitter user would be more likely than any non-UK Twitter user to see a tweet by the agency. On the Twitter platform, users had to actively choose to follow another user in order to automatically see that other user's tweets on their own feed. As the agency was advertised as a worldwide agency, there was no evidence that it was more likely to have active UK followers than active non-UK followers. There was also no evidence that UK Twitter users would be more likely than non-UK Twitter users to manually search for the agency's tweets.

Furthermore, Daiichi-Sankyo submitted that the two tweets were clearly posted from the conference in Spain and further the hashtags from the conference in Barcelona were used (#Barcelona and #ESCCongress). There was nothing contained within the tweets to suggest that a UK audience was targeted.

Furthermore, Daiichi-Sankyo submitted that the Panel's analysis that because a tweet came from an employee of a UK company, it was by default directed at a UK audience, was an incorrect interpretation. On this analysis, any UK third party company working with or for an international affiliate of a UK pharmaceutical company could not post material on the internet without it being deemed to be directed to a UK audience. This was surely not what was envisaged by Clause 28.1 of the Code which stated 'directed to a UK audience'. Just because the author of the tweet worked for a UK company could not infer or mean that the tweet was 'directed to a UK audience'. For this reason, Daiichi-Sankyo submitted that the tweets did not fall under the scope of the ABPI Code.

Summary of Appeal

Daiichi-Sankyo submitted that on the basis that the two tweets were not directed to a UK audience, they did not fall within the scope of the Code. Therefore Daiichi-Sankyo appealed all breaches (Clauses 7.9, 26.1, 26.2, 9.1 and 2) stemming from the tweets on the grounds that they were not within the scope of the ABPI Code.

Daiichi-Sankyo emphasised that it considered the seriousness of advertising medicines to the public and misleading the public about the safety of medicines. Daiichi-Sankyo did not engage in any of these activities, nor did it encourage any affiliate or agency to do so. Patient safety was at the forefront of Daiichi-Sankyo's activities. The agency tweets were sent without the knowledge of Daiichi-Sankyo's staff.

Clause 2

In relation to the tweets, Daiichi-Sankyo immediately brought the reported concerns to the attention of Daiichi-Sankyo Europe. Daiichi-Sankyo had, at all times, acted appropriately and responsibly to the concerns raised. In the circumstances, Daiichi-Sankyo's conduct did not amount to a breach of Clause 2.

Concerns of the Panel

Daiichi-Sankyo noted that the Panel was concerned about the continued use of #safeplicity by Daiichi-Sankyo Europe after Daiichi-Sankyo UK and the Alliance had raised concerns. Daiichi-Sankyo agreed that this was concerning. Daiichi-Sankyo UK now worked more closely with Daiichi-Sankyo Europe on the development of marketing campaigns and this increased collaboration would help to ensure messaging and materials were developed to a high ethical standard.

Daiichi-Sankyo noted that the Panel was concerned about the inadequate training given to UK staff manning the Daiichi-Sankyo Europe stand at ESC 2017. This concern had been taken on board by Daiichi-Sankyo, including the medical, compliance and marketing departments. In future, specific certified UK briefings would be given to any UK promotional staff attending international congress, specifying their obligations to adhere to the Code, and detailing any activities they should not be involved in.

In closing, Daiichi-Sankyo took patient safety very seriously and was committed to promoting the rational use of medicines and adhering to the Code.

COMMENTS FROM THE ALLIANCE

The Alliance agreed entirely with the decision of the Panel that pharmaceutical promotional material developed by a UK based agency, placed on the internet in the UK and published on the UK agency's Twitter account was intended for a UK audience and therefore fell within the scope of the Code. The ESC congress had a significant proportion of UK delegates and hence #safeplicity had a high likely exposure to a UK audience at the ESC as well as exposure to a UK audience in the UK.

The Alliance alleged that the fact that the hashtag #safeplicity was clearly designed to promote Lixiana despite the prohibited use of the word 'safe' which had not been disputed by Daiichi-Sankyo. The fact that it was used for this purpose had also been clearly demonstrated as had the fact that it was also used to promote a prescription medicine to

the general public in the UK. Thus, the findings of numerous Code breaches, and the sanctions associated with them, were correct, appropriate and necessary.

APPEAL BOARD RULING

The Appeal Board noted that it first needed to assess whether the tweets at issue were subject to the Code. The Appeal Board noted the requirements of Clause 28.2 and the role of Daiichi-Sankyo Europe which had employed the agency sending the tweets.

The Appeal Board did not consider that the two tweets at issue made specific reference to the availability or use of Lixiana in the UK. Taking all the circumstances into account, the Appeal Board considered that Clause 28.2 did not apply to the tweets, thus the ABPI Code did not apply. The Appeal Board ruled no breaches of Clauses 2, 7.9, 9.1, 26.1 and 26.2 because it considered that the matter of complaint did not fall within the scope of the Code. The appeal on this point was successful.

During its consideration the Appeal Board noted that the representatives from Daiichi-Sankyo UK agreed that the use of #safeplicity was unacceptable and that it had never and would never make use of this hashtag or any similar messaging. The safeplicity concept had been designed by an agency engaged by Daiichi-Sankyo Europe. The Appeal Board was very concerned about the use of #safeplicity by Daiichi-Sankyo Europe which continued after Daiichi-Sankyo UK and the Alliance had raised concerns. The Appeal Board considered that the use of #safeplicity would be unacceptable under the ABPI Code. Another code of practice would apply to the tweets. This was likely to be the German Code which, like the ABPI Code, was required to reflect the EFPIA Code.

Complaint received	**12 January 2018**
Undertaking received	**3 October 2018**
Appeal Board Consideration	**13 September, 17 October 2018**
Corrective Statement issued	**14 December 2018**

Daiichi-Sankyo sent the following Corrective Statement to recipients of the material at issue and relevant UK prescribers:

'Corrective statement

Between July 2016 and 20 August 2018, a Lixiana (edoxaban) Initiation Information Guide (ref EDX/16/0171) and/or a Lixiana Practical Guide (ref EDX/15/0091(4)) might have been provided to you by Daiichi-Sankyo UK Limited.

Section 4.4 of the Lixiana SPC, Special warnings and precautions for use, states under the sub heading 'Renal function in [nonvalvular atrial fibrillation] NVAF':

'A trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin (see section 5.1). Therefore, edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful evaluation of the individual thromboembolic and bleeding risk.

Assessment of renal function: CrCL should be monitored at the beginning of the treatment in all patients and afterwards when clinically indicated (see section 4.2).'

Daiichi-Sankyo apologises for the fact that the items at issue failed to include this warning other than in the prescribing information. Daiichi-Sankyo takes its responsibilities under the ABPI Code of Practice for the Pharmaceutical Industry and patient safety seriously and is disappointed at these failings. As an organisation we will take all possible steps to ensure that this is not repeated.

Following a complaint under the ABPI Code of Practice for the Pharmaceutical Industry, the Code of Practice Appeal Board ruled that the omission rendered the materials misleading and therefore the materials did not encourage the rational use of the medicine. The Appeal Board also ruled that Daiichi-Sankyo had failed to maintain high standards and had brought discredit upon and reduced confidence in the pharmaceutical industry. As a result of the above Daiichi-Sankyo has been required to issue this corrective statement and to refer to the published report for the case which contains full details. In addition Daiichi-Sankyo has been required to recover the material at issue. If you still have the material at issue please return it in the attached prepaid envelope as soon as possible.

Details of this case (Case AUTH/3010/1/18) are also available on the PMCPA website (www.pmcpa.org.uk).'