CASES AUTH/3215/6/19 and AUTH/3216/6/19

GP v PFIZER AND BRISTOL-MYERS SQUIBB

Promotion of Eliquis

A general practitioner complained about a page of an Eliquis (apixaban) six-page, landscape, gatefold leavepiece (ref PP-ELI-GBR-4453) issued by Pfizer Limited and Bristol-Myers Squibb Pharmaceuticals Limited. Eliquis was a non-vitamin K antagonist oral anticoagulant (NOAC) indicated, *inter alia*, for the prevention of stroke and systemic embolism in certain adults with non-valvular atrial fibrillation (NVAF).

The complainant provided a page of the leavepiece headed 'Eliquis is the only factor Xa inhibitor that does not require a dose adjustment in patients with NVAF who have mild or moderate renal impairment[2*]'. The page included a table which compared the dose adjustment required depending on degree of renal impairment when prescribing Eliquis vs rivaroxaban, edoxaban and dabigatran. The table showed that no dose adjustment was needed for Eliquis in patients with mild to moderate renal impairment or normal renal function. Low dose was required in severe renal impairment and Eliquis was not recommended in renal failure/dialysis. An asterisk appeared next to the headline and the 'no dose adjustment' statement for Eliquis within the table which took the reader to a footnote which read: 'Dose reduction to Eliquis 2.5mg bd is recommended in patients with NVAF who meet two or more of the following criteria: ≥ 80 years, body weight ≤ 60kg, or serum creatinine ≥ 1.5 mg/dl (133μmol/l). Patients with exclusive criteria of severe renal impairment (CrCl 15-29ml/min) should also receive a lower dose of 2.5mg bd. Eliquis is not recommended for patients with CrCl<15ml/min'. The statement was referenced to the Eliquis summary of product characteristics (SPC).

The complainant alleged that the page was misleading and had potential to lead to patient harm if dose adjustments were not made to Eliquis according to its licence. The way the leavepiece was written might lead clinicians who did not notice the tiny asterisk to ignore dose adjustment that was necessary dependent on the patient's creatinine clearance, age, creatinine level and weight.

In the complainant's view, the leavepiece was designed to give unfair advantage over competitor medicines and he/she saw no reason for the companies to specifically highlight edoxaban (Lixiana, marketed by Daiichi-Sankyo) yet not highlight the need for dose adjustment with Eliquis. In the complainant's view this was an example of aggressive and misleading marketing that could lead to inaccurate dosing with potential for either increased bleed risk or stroke in inappropriately dosed atrial fibrillation patients.

The detailed response from Pfizer and Bristol-Myers Squibb (the Alliance) is given below.

The Panel noted the Alliance's submission about the layout and flow of the leavepiece and the way in which the pages of the gatefold leavepiece were likely to be read. There was no evidence before the Panel about the order in which recipients would read the leavepiece. Whilst context and flow of information was important the Panel noted that each page ought to stand alone with regards to the requirements of the Code – they

could not rely on qualification necessary for Code compliance on either a separate page or a footnote.

The Panel noted the Alliance's submission that the layout was designed to ensure that recipients viewed a page which included Eliquis data and licensed dosing requirements in the overarching NVAF patient population before viewing the dosage recommendations according to renal function which was presented in the context of the recommendations for the three other medicines in the NOAC class.

The Panel considered that although readers would likely see the bottom panel of view 2/outside back page when first opening the gatefold leavepiece, a reasonable number would read the detail of the inside triple page spread first, the last page of which included the detailed dosage recommendations in patients with NVAF according to renal function for the four NOACs in a tabular format which was the subject of complaint.

The Panel noted that according to its SPC the recommended dose of Eliquis for the prevention of stroke and systemic embolism in patients with NVAF was 5mg taken orally twice daily. A dose reduction of 2.5mg taken orally twice daily was recommended in patients with NVAF who had at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60kg, or serum creatinine ≥ 1.5mg/dL (133 micromole/L).

Section 4.2 of the Eliquis SPC 'Renal impairment' stated: 'In patients with mild or moderate renal impairment, the following recommendations apply: for the prevention of stroke and systemic embolism in patients with NVAF and serum creatinine ≥1.5 mg/dL (133 micromole/L) associated with age ≥80 years or body weight ≤60 kg, a dose reduction is necessary and described above. In the absence of other criteria for dose reduction (age, body weight), no dose adjustment is necessary (see section 5.2)'.

In the Panel's view, the table at issue which stated that no dosage adjustment for Eliquis was required in NVAF patients with normal renal function or mild or moderate renal impairment would be read in conjunction with the prominent headline claim 'Eliquis is the only factor Xa inhibitor that does not require a dose adjustment in patients with NVAF who have mild or moderate renal impairment' and implied that no dosage adjustment for Eliquis was needed in all NVAF patients with mild to moderate renal impairment which was not so.

The Panel considered the immediate impression of the table to a busy health professional was misleading. The footnote in very small font at the very bottom of the page in question, and the data and licensed dosing requirements for Eliquis in the overarching NVAF patient population on a separate page of the leavepiece were wholly insufficient to qualify the misleading impression given about Eliquis dosing in NVAF patients with normal renal function and mild or moderate renal impairment. A breach of the Code was ruled.

The Panel considered that the dosing information within the table and associated headline claim did not accurately reflect the dosage recommendations in the Eliquis SPC for NVAF patients with normal renal function or mild and moderate renal impairment. A breach of the Code was ruled.

With regard to the allegation that the page in question was designed to give an unfair advantage over competitor medicines, the Panel noted that the table at issue stated that no dose adjustment was required in NVAF patients with normal renal function or mild renal impairment for any of the four NOACs.

The Panel noted that for moderate renal impairment low dose was recommended for rivaroxaban and edoxaban. No dose adjustment was stated for Eliquis which was highlighted green, whereas no dose adjustment for dabigatran was highlighted orange and further stated below '(Consider 100mg BD in patients with high bleeding risk)'.

The Panel noted that rivaroxaban was the only NOAC that did not have an asterisk next to the no dosage adjustment statement within the table. It considered the explanations for the various asterisks.

The Panel noted that other than for rivaroxaban, each reference to no dose adjustment within the table was similarly misleadingly qualified by a footnote. The Panel noted, however, that the table and headline misleadingly implied that Eliquis was the only NOAC for which no dose adjustment was required in NVAF patients with moderate renal impairment, which was not so; a dosage reduction for Eliquis was recommended in certain NVAF patients with moderate renal impairment as noted above. Noting its comments above the Panel considered that the comparison was misleading, and a breach of the Code was ruled.

The Panel considered that the Alliance had failed to maintain high standards and a breach of the Code was ruled. Upon appeal by the Alliance, the Appeal Board noted that some busy health professionals might read the page at issue without necessarily reading the leavepiece as intended by the Alliance. When viewed in isolation the table and page at issue were insufficient for a health professional to make an appropriate prescribing decision. The Appeal Board considered that there had been a failure to maintain high standards and it upheld the Panel's ruling.

The Panel noted the complainant's concern about the potential for increased bleeding risk or stroke in inappropriately dosed patients. The Panel considered that patient safety was of the utmost importance and the Alliance's failure in this regard brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled which was upheld on appeal by the Alliance.

A general practitioner complained about a page of an Eliquis (apixaban) six-page, landscape, gatefold leavepiece (ref PP-ELI-GBR-4453) issued by Pfizer Limited and Bristol-Myers Squibb Pharmaceuticals Limited. Eliquis was indicated, *inter alia,* for the prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA), age ≥ 75 years, hypertension, diabetes or symptomatic heart failure (NYHA class ≥II).

The complainant provided a page of the leavepiece headed 'Eliquis is the only factor Xa inhibitor that does not require a dose adjustment in patients with NVAF who have mild or moderate renal impairment[2*]'. The page included a table which compared the dose adjustment required depending on degree of renal impairment (mild, moderate, severe, renal failure/dialysis) when prescribing Eliquis vs rivaroxaban, edoxaban and dabigatran. The table

showed that no dose adjustment was needed for Eliquis in patients with mild to moderate renal impairment or normal renal function. Low dose was required in severe renal impairment and Eliquis was not recommended in renal failure/dialysis. An asterisk appeared next to the headline and the 'no dose adjustment' statement for Eliquis within the table which took the reader to a footnote which read: 'Dose reduction to Eliquis 2.5mg bd is recommended in patients with NVAF who meet two or more of the following criteria: ≥ 80 years, body weight ≤ 60kg, or serum creatinine ≥ 1.5 mg/dl (133µmol/l). Patients with exclusive criteria of severe renal impairment (CrCl 15-29ml/min) should also receive a lower dose of 2.5mg bd. Eliquis is not recommended for patients with CrCl<15ml/min'. The statement was referenced to the Eliquis summary of product characteristics (SPC).

COMPLAINT

The complainant alleged that the page provided was misleading and had potential to lead to patient harm if dose adjustments were not made to Eliquis according to its licence. The way the leavepiece was written might lead clinicians who didn't notice the tiny asterisk to ignore dose adjustment that was necessary dependent on the patient's creatinine clearance, age, creatinine level and weight.

In the complainant's view, the leavepiece was designed to give unfair advantage over competitor medicines and he/she saw no reason to specifically highlight edoxaban (Lixiana, marketed by Daiichi-Sankyo) yet not highlight the need for dose adjustment with Eliquis. In the complainant's view this was an example of aggressive and misleading marketing that could lead to inaccurate dosing with potential for either increased bleed risk or stroke in inappropriately dosed atrial fibrillation patients.

The complainant stated that several of his/her GP cardiology and diabetes colleagues who had seen the leavepiece agreed and the complainant requested that the leavepiece be withdrawn and the companies sanctioned.

The complainant provided for comparison a copy of a GP notebook shortcuts page headed 'Direct Oral Anticoagulant (DOAC) Dosing for Stroke Prevention in those with Non-Valvular Atrial Fibrillation' which compared the dosing of apixaban, dabigatran, edoxaban and rivaroxaban in relation to creatinine clearance.

When writing to Pfizer and Bristol-Myers Squibb, the Authority asked them to consider the requirements of Clauses 2, 3.2, 7.2, 7.3 and 9.1 of the Code.

RESPONSE

Pfizer responded on behalf of the Pfizer/Bristol-Myers Squibb Alliance (the Alliance) and submitted that the leavepiece at issue was intended for distribution by representatives and from exhibition stands. The leavepiece provided information on the key safety and efficacy data from the ARISTOTLE study, a Phase III randomised controlled trial of Eliquis in patients with NVAF, including a sub-analysis based on renal function. The leavepiece, certified in January 2019, had been withdrawn due to a recent change to the Eliquis prescribing information.

The Alliance provided an illustration which set out the layout and explained the flow of the leavepiece and the order in which the information would be viewed by the recipient.

View 1:
The leavepiece was presented as a folded A5 piece.

- Front panel: Described the licensed indication for Eliquis in patients with NVAF.
- Back panel: Contained prescribing information and other obligatory information.

View 2:
Consisted of the two panels that were accessed by lifting the front panel of the leavepiece.

- Top panel: Provided an overview of key safety and efficacy outcomes of the registrational Phase III randomised control trial in patients with NVAF.
- Bottom panel: Presented a prominent and detailed description of the licensed dosage reduction criteria for Eliquis in patients with NVAF. A combination of imagery and large font size was used to ensure that the recipient was made aware of the dosage guidance before accessing further information contained within the piece.

View 3:
Consisted of the three panels accessed by folding down the bottom panel of view 2.

- Top panel: This was the same top panel as seen in view 2 which provided an overview of key safety and efficacy outcomes of the registrational Phase III trial in patients with NVAF.
- Centre panel: Provided an overview of the key safety and efficacy outcomes in relation to renal function based on a sub-analysis from the registrational Phase III trial in patients with NVAF.
- Bottom panel: Detailed dosage recommendations according to renal function for the four non-vitamin K antagonist oral anticoagulants (NOACs).

The piece was designed to ensure that the recipient viewed the data and licensed dosing requirements for Eliquis in the overarching NVAF patient population before viewing the specific renal data and associated dosing recommendation according to renal function for Eliquis, which was presented in the context of the recommendations for the three other medicines in the NOAC class.

With regard to the requirements of Clause 3.2, the Alliance noted that the front panel, (view 1) of the leavepiece described the licensed indication for Eliquis as being for 'the prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II)'. This was in accordance with the terms of the Eliquis marketing authorization and consistent with the Eliquis SPC (copy provided).

The Alliance submitted that detailed and clear dosing guidance was prominently displayed in view 2 of the leavepiece. This was consistent with Section 4.2 of the Eliquis SPC which stated: 'The recommended dose of apixaban is 5mg taken orally twice daily. The recommended dose of apixaban is 2.5mg taken orally twice daily in patients with NVAF and at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60kg, or serum creatinine ≥ 1.5mg/dL (133micromole/L)'.

The dosage recommendations for Eliquis according to renal function was preceded by the overarching dosing considerations described above. The dosage guidance for Eliquis according

to renal function as shown in the table on the bottom panel of view 3, was consistent with Section 4.2 of the Eliquis SPC which stated that 'In patients with mild or moderate renal impairment, the following recommendations apply: for the prevention of stroke and systemic embolism in patients with NVAF and serum creatinine ≥1.5mg/dL (133micromole/L) associated with age ≥80 years or body weight ≤60kg, a dose reduction is necessary and described above. In the absence of other criteria for dose reduction (age, body weight), no dose adjustment is necessary (see section 5.2)'.

All information provided in the leavepiece was in accordance with the terms of the Eliquis marketing authorization and was not inconsistent with the SPC. The Alliance therefore denied a breach of Clause 3.2.

With regard to Clauses 7.2 and 7.3, the Alliance submitted that the leavepiece provided a balanced overview of the therapeutic indication, dosing information, safety and efficacy data for Eliquis, and enabled the recipient to make an appropriate assessment of the therapeutic value of the medicine based on the leavepiece as a standalone item. The licensed dose reduction criteria for Eliquis in patients with NVAF was clearly and prominently stated on the bottom panel of view 2 of the leavepiece. The layout of the leavepiece required readers to view this information before accessing any further information contained within the piece. The same dosing information was also repeated as a footnote to the NOAC renal function dosage recommendation table on the bottom panel of view 3. These provisions ensured that recipients were provided with accurate, unambiguous Eliquis dosing information to support their review of the NOAC renal function dosage recommendation table.

The Alliance submitted that it was appropriate to summarise the dosage recommendations according to renal function for the four NOACs in a single table as they were all licensed for the prevention of stroke and systemic embolism in adults with NVAF and one or more risk factors. The data contained within the table was accurate and consistent with the respective SPCs of each NOAC.

The Alliance noted that the Lixiana SPC (copy provided) included the following special warning and precaution for patients with high creatinine clearance: '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 noted that Lixiana was the only NOAC to have such precautionary wording for patients with high creatinine clearance included in its SPC. It was therefore considered to be accurate and fair to include this important warning in the panel summarising the renal dosing considerations for the NOAC class of medicines.

The Alliance submitted that the information presented in the table displayed in the bottom panel of view 3 of the leavepiece was accurate, fair and balanced for the four medicines in the NOAC class. The comparison presented in the table was not misleading and the information was relevant and substantiable. The leavepiece was consistent with all requirements of Clauses 7.2 and 7.3.

The Alliance strongly refuted the suggestion that the leavepiece might cause clinicians to overlook the required dosage adjustments for Eliquis and potentially cause harm to patients. The leavepiece had been carefully designed to ensure that the overarching dosage adjustment information for Eliquis was prominently displayed in a dedicated panel which the reader must

view before moving to the subsequent panel focusing on renal dosing. The same dosage adjustment information for Eliquis was then repeated in a footnote in the subsequent panel focusing on renal dosing. The Alliance regarded this as a responsible and appropriate way to communicate this important information.

The Alliance considered that the leavepiece was of a high standard and did not bring discredit upon or reduce confidence in the industry.

PANEL RULING

The Panel noted the Alliance's submission about the layout and flow of the leavepiece and the way in which the pages of the gatefold leavepiece were likely to be read. There was no evidence before the Panel about the order in which recipients would read the leavepiece. Whilst context and flow of information was important the Panel noted that each page ought to stand alone with regards to the requirements of the Code.

The Panel noted the Alliance's submission that the bottom panel of view 2, which might be considered by some as the outside back page, included a description of the licensed dosage criteria for Eliquis in patients with NVAF stating, 'Only use Eliquis 2.5mg BD in patients with NVAF who: meet two or more of the dose reduction criteria which were age ≥ 80 years; body weight ≤ 60kg and creatinine ≥ 1.5mg/dl (133 µmol/l) OR have severe renal impairment (CrCl 15-29 ml/min) alone'. This was referenced to the Eliquis SPC. The Panel noted the Alliance's submission that the layout was designed to ensure that the recipient viewed this page which included data and licensed dosing requirements for Eliquis in the overarching NVAF patient population before viewing the dosage recommendations for Eliquis according to renal function which was presented in the context of the recommendations for the three other medicines in the NOAC class.

The Panel considered that although readers would likely see the bottom panel of view 2/ outside back page described above when first opening the gatefold leavepiece, a reasonable number would read the detail of the inside triple page spread first, the last page of which included the detailed dosage recommendations in patients with NVAF according to renal function for the four NOACs in a tabular format which was the subject of complaint. In any event it was a well-established principle that each page of the leavepiece had to be capable of standing alone with regard to the requirements of the Code and could not rely on qualification necessary for Code compliance on either a separate page or a footnote.

The Panel noted that according to its SPC, the recommended dose of Eliquis for the prevention of stroke and systemic embolism in patients with NVAF was 5mg taken orally twice daily. A dose reduction of 2.5mg taken orally twice daily was recommended in patients with NVAF who had at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60kg, or serum creatinine ≥ 1.5mg/dL (133micromole/L).

Section 4.2 of the Eliquis SPC 'Renal impairment' stated that 'In patients with mild or moderate renal impairment, the following recommendations apply: for the prevention of stroke and systemic embolism in patients with NVAF and serum creatinine ≥1.5 mg/dL (133 micromole/L) associated with age ≥80 years or body weight ≤60 kg, a dose reduction is necessary and described above. In the absence of other criteria for dose reduction (age, body weight), no dose adjustment is necessary (see section 5.2)'.

In the Panel's view the table at issue which stated that no dosage adjustment for Eliquis was required in NVAF patients with normal renal function or mild or moderate renal impairment would be read in conjunction with the prominent headline claim 'Eliquis is the only factor Xa inhibitor that does not require a dose adjustment in patients with NVAF who have mild or moderate renal impairment' and implied that no dosage adjustment for Eliquis was needed in all NVAF patients with mild to moderate renal impairment which was not so. In that regard, the Panel also noted the GP notebook shortcuts page provided by the complainant which showed the 5mg twice daily or 2.5mg twice daily dose for mild and moderate renal impairment.

The Panel considered the immediate impression of the table to a busy health professional was misleading. The footnote, in very small font at the very bottom of the page in question, and the data and licensed dosing requirements for Eliquis in the overarching NVAF patient population on a separate page of the leavepiece, were wholly insufficient to qualify the misleading impression given about Eliquis dosing in NVAF patients with normal renal function and mild or moderate renal impairment. A breach of Clause 7.2 was ruled.

The Panel noted that Clause 3.2 of the Code stated that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its SPC.

The Panel considered that the dosing information within the table and associated headline claim, was not an accurate reflection of the dosage recommendations in the Eliquis SPC for NVAF patients with normal renal function, or mild and moderate renal impairment, and was therefore inconsistent with the SPC. The Panel ruled a breach of Clause 3.2.

The Panel noted the complainant's allegation that the page in question was designed to give an unfair advantage over competitor medicines. In particular the complainant saw no reason for the companies to specifically highlight edoxaban (Lixiana) yet not highlight the need for dose adjustment with Eliquis.

The Panel noted that the table at issue stated that no dose adjustment was required in NVAF patients with normal renal function or mild renal impairment for any of the four NOACs.

The Panel noted that for moderate renal impairment low dose was recommended for rivaroxaban and edoxaban. No dose adjustment was stated for Eliquis which was highlighted green, whereas no dose adjustment for dabigatran was highlighted orange and further stated below '(Consider 100mg BD in patients with high bleeding risk)'.

The Panel noted that rivaroxaban was the only NOAC that did not have an asterisk next to the no dosage adjustment statement within the table.

The Panel noted that the asterisk for edoxaban took the reader to a footnote which read: 'Dose reduction to edoxaban 30mg OD is recommended in patients with NVAF with one or more of the following clinical factors: moderate or severe renal impairment; low body weight ≤ 60kg; concomitant use of the following P-gp inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole'. The Panel further noted that below the no dose adjustment for normal renal function for edoxaban was the statement 'Careful evaluation is required in patients with high CrCl)' followed by two asterisks which stated: 'Edoxaban should only be used in patients with NVAF and high CrCl after a careful evaluation of the individual thromboembolic and bleeding risk, due to an observed trend towards decreasing efficacy and increasing CrCl for edoxaban

vs. well-managed warfarin' and 'In ENGAGE AF-TMI, there was a statistically significant interaction between the effect of edoxaban vs warfarin on the main study outcome (stroke/systemic embolism) and renal function (p-value 0.0042; mITT, overall study period)' respectively.

The Panel noted the Alliance's submission that Lixiana (edoxaban) was the only NOAC to have such precautionary wording for patients with high creatinine clearance included in its SPC and it therefore considered it accurate and fair to include it within the table summarising the renal dosing considerations for the NOAC class of medicines.

The asterisk for dabigatran took the reader to a footnote which read: 'The lower dose of dabigatran 110mg BD is recommended for patients with NVAF who meet one or more of the following criteria: ≥80 years; receiving concomitant verapamil For the following groups, the daily dose of dabigatran of 300mg or 220mg (150mg BD or 110mg BD) should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding: patients between 75-80 years; patients with moderate renal impairment; patients with gastritis, oesophagitis or gastro-oesophageal reflux; other patients at increased risk of bleeding. Close clinical surveillance is recommended in patients with renal impairment'.

The Panel noted that other than for rivaroxaban, each reference to no dose adjustment within the table was similarly misleadingly qualified by a footnote. The Panel noted, however, that the table and headline misleadingly implied that Eliquis was the only NOAC for which no dose adjustment was required in NVAF patients with moderate renal impairment, which was not so; a dosage reduction for Eliquis was recommended in certain NVAF patients with moderate renal impairment as noted above. Noting its comments above the Panel considered that the comparison was misleading, and a breach of Clause 7.3 was ruled.

The Panel considered that the Alliance had failed to maintain high standards and a breach of Clause 9.1 was ruled. This ruling was appealed by the Alliance.

The Panel noted the complainant's concern about the potential for increased bleeding risk or stroke in inappropriately dosed patients. The Panel considered that patient safety was of the utmost importance and the Alliance's failure in this regard brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled. This ruling was appealed by the Alliance.

APPEAL BY THE ALLIANCE

In light of the Panel's rulings, the Alliance recognised that the table and information in panel 5 of the leavepiece could have been presented in a better way to ensure that if viewed in isolation from the rest of the leavepiece, no confusion would be caused. The Alliance accepted breaches of Clauses 3.2, 7.2, and 7.3 in that regard.

The Alliance however submitted that the leavepiece contained all the information necessary for Eliquis to be used safely and rationally, in accordance with its approved SPC. When the leavepiece was viewed in the way that it was designed and intended it to be viewed, recipients would have received all of the relevant Eliquis dosing information required to ensure patient safety was not compromised; the design features of the leavepiece supported and demonstrated this. The Alliance highlighted the steps that it had already taken as part of its ongoing continuous improvement activities and was confident that these actions had ensured

that no further confusion could have been caused by the renal dosing table following the withdrawal of the leavepiece in June 2019. The Alliance submitted that these points demonstrated that it had maintained high standards in relation to the leavepiece and that it had not brought discredit upon or reduced confidence in the pharmaceutical industry. The Alliance therefore respectfully appealed the Panel's rulings of a breach of Clause 9.1 and Clause 2.

The Alliance reiterated that the item at issue was a six-panel, folded leavepiece intended for distribution by representatives and from exhibition stands. The leavepiece provided information on the key safety and efficacy data from the ARISTOTLE study, a Phase III randomised control trial (RCT) of Eliquis in patients with NVAF, including a sub-analysis based on renal function.

The Alliance submitted that one of the objectives of the leavepiece was to communicate the dosage recommendations for the use of Eliquis in patients with NVAF, specifically in relation to renal function. Available data at the time suggested inappropriate underdosing with the 2.5mg dose of Eliquis in patients with NVAF. The Alliance was concerned that a proportion of those patients might not satisfy the necessary dose reduction criteria as specified in the licensed indication, based on descriptive data from European and US data sets and local prescribing data. As a result, the leavepiece was carefully designed with the intent to first present the dosage guidance in the context of the broader NVAF population, before focusing on the dosage guidance in relation to renal impairment. The leavepiece was intended to guide recipients through firstly assessing whether a patient met two or more of the Eliquis standard dose-reduction criteria (age ≥ 80 years, body weight ≤ 60kg or creatinine ≥1.5mg/dl) before secondly considering whether any other adjustment was required based on renal function alone. Underdosing of Eliquis in patients with mild to moderate renal impairment alone could potentially lead to an increased risk of stroke and so the flow and design features of the leavepiece were purposely put in place in order to clarify this issue.

The Alliance disagreed with the Panel's ruling that there was no evidence about the order in which recipients would read the leavepiece. The leavepiece was printed and folded by the print house prior to provision to Alliance colleagues for onward distribution. The leavepiece was provided to health professionals in this folded format which was carefully designed to lead the recipient through the information in a specific sequence delivering a balanced summary of key efficacy and dosing information. It was impossible to open the leavepiece in any other order than that intended by the Alliance.

The Alliance provided an illustration of the layout of the leavepiece and the order in which the information would be viewed by the recipient.

View 1:

The leavepiece was presented as a folded A5 piece.

- Front panel (panel 1): Described the licensed indication for Eliquis in patients with NVAF.
- Back panel (panel 6): Contained prescribing information and other obligatory information.

View 2:

Consisted of two panels that were accessed by lifting the front panel of the leavepiece:

- Top panel (panel 2): Provided an overview of key safety and efficacy outcomes of the registrational Phase III RCT in patients with NVAF.
- Bottom panel (panel 3): Presented a prominent and detailed description of the licensed dosage reduction criteria for Eliquis in patients with NVAF. A combination of imagery and large font size was used to ensure that the recipient was made aware of this dosage guidance before accessing further information in the leavepiece.

View 3:

Consisted of three panels accessed by folding down the bottom panel of view 2.

- Top panel (panel 2): This was the same top panel as seen in view 2 which provided an overview of key safety and efficacy outcomes of the registrational Phase III RCT in patients with NVAF.
- Centre panel (panel 4): Provided an overview of the key safety and efficacy outcomes in relation to renal function based on a sub-analysis from the registrational Phase III RCT in patients with NVAF.
- Bottom panel (panel 5): Detailed dosage recommendations according to renal function for the four non-vitamin K antagonist oral anticoagulants (NOACs).

The Alliance submitted that the folded format of the leavepiece prevented health professionals from accessing the detailed renal subgroup information before they had received the key dosing and registrational efficacy and safety information applicable to the overarching NVAF population. An entire panel of the leavepiece was dedicated to communicating the licensed dosage recommendations for the overarching NVAF population. A combination of imagery and large font size was used to ensure that recipients did not miss the significance of this content. Should recipients move through the leavepiece quickly, they would have still seen the prominent standard dosing and reduced dosing criteria for Eliquis before viewing the renal information. It would be impossible to view the internal renal panels without first, at the very least, briefly seeing the prominent dose reduction information on panel 3. The dose reduction information was then repeated as a footnote to the renal table on panel 5. This footnote was never intended to be the sole source of dosing information qualifying the renal table. It was always expected that the design of the leavepiece would ensure that all recipients were fully aware of the dose reduction criteria for Eliquis before considering any additional implications of renal impairment on Eliquis dosing.

The Alliance disagreed that the dosing panel could ever be considered the outside back-page of the leavepiece, as if this were the case, the dosing panel would be upside down relative to the prescribing information, clearly indicating that this was not the intended way of viewing the panel.

The Alliance was concerned about the PMCPA's suggestion that panels in a leavepiece created from a single piece of card, with a clearly defined flow, could not rely upon information presented in a clear and prominent manner earlier in the leavepiece. This potentially had implications for the use of any multi-page leavepiece in the promotion of medicines.

Given the format of the leavepiece and the flow of information, the Alliance believed that it was clear that it had intended the information to be received in a specified order and had taken appropriate measures to make certain that the leavepiece could only be viewed in that order,

ensuring that recipients were fully aware of the Eliquis dosing recommendations before accessing the renal information.

The Alliance submitted that on 21 June 2019, the leavepiece was withdrawn from use due to the need to update the Eliquis prescribing information. The Alliance took this opportunity to not only update the prescribing information, but as part of its continuous improvement activities, to also review and enhance the content. The updated leavepiece (ref PP-ELI- GBR-5598) was approved for use on 12 July 2019 and had been in circulation since then. Whilst the Alliance submitted that the original leavepiece, if viewed as intended, provided accurate guidance on the dosing of Eliquis, the clarity of the renal table had been improved in the new leavepiece. This action was taken independently of the current complaint. Accordingly, the Alliance believed that these actions demonstrated its commitment to maintaining high standards and not bringing discredit upon the industry.

COMMENTS FROM THE COMPLAINANT

The complainant stated that he/she had nothing to add to his/her original submission and still maintained that the leavepiece was very misleading and could potentially cause patient harm.

APPEAL BOARD RULING

The Appeal Board noted that the Alliance had accepted that the table detailing NOAC dosage recommendations in patients with NVAF across renal function levels, and information presented on the page in question in the leavepiece, could have been presented in a better way to ensure that if viewed in isolation from the rest of the leavepiece, no confusion would be caused. The Alliance submitted that it had started to revise the leavepiece, independently of the complaint and it had been withdrawn in June 2019 in relation to a prescribing information update. The Appeal Board noted that the revised leavepiece, which was not at issue in this case, included significant changes to the leavepiece at issue and further noted the submission of the company representatives at the appeal that the revised table included all relevant dosing information in case it was viewed in isolation.

The Appeal Board noted that a busy health professional might scan a leavepiece and only read certain parts. It was likely that some health professionals would be drawn to the table in question without necessarily reading the leavepiece as intended by the Alliance. The table used a traffic light system of colours (green, amber and red). The Appeal Board considered that this would encourage health professionals to consider that there was no need to adjust the dose when using Eliquis in patients with normal, mild or moderate renal impairment, all shaded green for go, which was not so. Prescribers still needed to bear in mind the need for dose reduction if patients met two or more of the age, body weight and serum creatinine criteria. The Appeal Board noted that there were potential patient safety issues with both overdosing and underdosing of Eliquis.

The Appeal Board noted that the Alliance had accepted the Panel's rulings of breaches of the Code above in that the table and page at issue in the leavepiece were misleading and inconsistent with the Eliquis SPC as they implied that no dosage adjustment for Eliquis was needed in all NVAF patients with mild to moderate renal impairment which was not so. In addition, the Alliance accepted that the table also misleadingly implied that Eliquis was the only NOAC for which no dose adjustment was required in NVAF patients with moderate renal impairment, which was not so. The Appeal Board considered the sequence of flow and context

of information in the leavepiece was important and noted its comments above about how a health professional might look at the material. However, when viewed in isolation the table and page at issue in the leavepiece was insufficient for a health professional to make an appropriate prescribing decision. The Appeal Board considered that the Panel's rulings amounted to a failure to maintain high standards and consequently upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

Both under and overdosing of Eliquis had critically important patient safety outcomes and in this regard the Appeal Board noted the complainant's concern about the potential for increased bleeding risk or stroke in inappropriately dosed patients. The Appeal Board considered that patient safety was of the utmost importance and the Alliance's failure in this regard brought discredit upon and reduced confidence in the pharmaceutical industry. Consequently, the Appeal Board upheld the Panel's ruling of a breach of Clause 2. The appeal on this point was unsuccessful.

Complaint received **21 June 2019**

Case completed **13 May 2020**