CASE AUTH/3246/9/19 and AUTH/3247/9/19

COMPLAINANT v PFIZER AND BRISTOL-MYERS SQUIBB

Promotion of Eliquis

A complainant who described himself/herself as a concerned UK health professional, complained about the promotion of Eliquis (apixaban) by Pfizer Limited and Bristol-Myers Squibb Pharmaceuticals Limited. The material at issue appeared on the Pulse website (Pulsetoday.co.uk). Eliquis was indicated, *inter alia*, for the prevention of stroke and other vascular emergencies in adults such as deep vein thrombosis (DVT) and pulmonary embolism (PE).

The complainant explained that he/she had received a promotional email with the subject heading 'Clot Busting – DVT/PE management at your fingertips [BMS/Pfizer Alliance funded content]'. There was nothing to indicate what medicine was at issue and there was no prescribing information in the email itself. There was nothing on the linked webpage to prevent those who were not health professionals from seeing it.

The complainant also noted the claim that 'Eliquis can be used in a broad range of patients with VTE with no dose adjustments regardless of age, weight or renal function*'. The asterisk led to a statement which read 'Eliquis should be used with caution in patients with severe renal impairment (CrCl 15-29ml/min) for both the treatment of DVT/PE and prevention of recurrent DVT/PE. Eliquis is not recommended in patients with CrCl<15ml/min, or in patients undergoing dialysis'. The complainant stated that thus, there clearly were dose adjustments.

The complainant recalled that a previous Eliquis advertisement failed to mention patients with lower eGFR. The complainant accepted that there was clarification in smaller text but given that most readers would not focus on the detail, the header of 'no dose adjustments' would be the main message. There were many contraindications listed in the summary of product characteristics (SPC) which were not mentioned in the 'broad range of patients'. These were patient safety issues as the information was misleading.

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

The Panel noted that the email received by the complainant with the subject line 'Clot Busting – DVT/PE management at your fingertips [BMS/Pfizer Alliance funded content]' was, according to the Alliance, not the final certified version provided to Pulse. The Panel noted the Alliance's submission that the email sent by Pulse differed from the final certified form with regard to the subject line and the date of preparation only; the content was the same as the certified version.

The Panel noted that the subject line of the email received by the complainant included the claim 'Clot busting' and the email referred to DVT/PE management, anticoagulation

treatment and the BMS/Pfizer Alliance which marketed Eliquis, an anticoagulant used for, *inter alia*, the treatment of DVT/PE. Noting the broad definition of promotion in the Code, the Panel considered that the email was promotional. In that regard, the Panel noted that at the outset of the email, a prominent statement read 'This email contains promotional content that has been developed and funded by the Bristol-Myers Squibb / Pfizer Alliance ….'. In the Panel's view, given that readers might not click through to the Pulse website, the email should be capable of standing alone with regard to the requirements of the Code. The Panel ruled a breach in relation to the email and the failure to provide Eliquis prescribing information. Upon appeal, the Appeal Board considered that the email was promotional and in any event was inextricably linked to the promotional webpages. The Appeal Board consequently upheld the Panel's ruling.

The Panel noted that in the screenshot provided by the complainant the claim 'Eliquis can be used in a broad range of patients with VTE [venous thromboembolism] with no dose adjustments regardless of age, weight or renal function*' appeared in the section of the website entitled 'Eliquis in VTE' below the emboldened heading in dark blue font 'No dose adjustments'. The asterisk led the reader to a statement immediately beneath in smaller italic font which read 'Eliquis should be used with caution in patients with severe renal impairment (CrCl 15-29ml/min) for both the treatment of DVT/PE and prevention of recurrent DVT/PE. Eliquis is not recommended in patients with CrCl<15ml/min, or in patients undergoing dialysis'. The Panel noted that following this was a table which summarised the dosing considerations of the four non-vitamin K antagonist oral anticoagulants (NOACs) by age, weight and renal function.

The Panel noted the layout of the relevant webpages which were, in its, designed to be viewed digitally. The Panel queried how the information would be viewed on different devices and if the text within the table would be legible across different platforms/devices particularly a mobile phone. It appeared to the Panel that the site made use of infinite scrolling which was a web-design technique that loaded content continuously as the user scrolled down the page, eliminating the need for pagination. In the Panel's view, some readers might have read the claim at issue without scrolling down further to see the footnote or table, or scroll directly past the footnote and table particularly noting that it appeared from the headline and claim that Eliquis could be used in a broad range of patients with VTE and there were no dosage adjustments or concerns with regards to patients with impaired renal function.

The Panel noted that Section 4.2 of the Eliquis SPC stated that for VTEt no dose adjustment was required for body weight, gender or the elderly. The Panel noted that Section 4.2 stated under the heading 'Renal impairment' that for the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt): in patients with mild or moderate renal impairment no dose adjustment was necessary; in patients with severe renal impairment (creatinine clearance 15-29ml/min) apixaban was to be used with caution; and in patients with creatinine clearance <15 ml/min, or in patients undergoing dialysis, there was no clinical experience therefore apixaban was not recommended.

The Panel noted the Alliance's submission that as there were no contraindications related to the age and weight of VTE patients, Eliquis could be prescribed in a broad range of patients. The Panel disagreed with the Alliance's submission that the recommendations for patients with severe renal impairment (creatinine clearance 15-29ml/min) and in patients with creatinine clearance <15 ml/min, or in patients undergoing

dialysis did not equate to dose adjustments and therefore the claim at issue was not misleading. The Panel noted that these recommendations were included in Section 4.2 of the SPC which dealt with posology and method of administration and were included in the table referred to above which summarised the dosing considerations of the four NOACs by age, weight and renal function. In the Panel's view, the recommendations therefore would be considered within the context of dose adjustments and the fact that a medicine should only be used with caution or not at all in patients with VTE and certain levels of renal impairment was relevant and important information; it might mean that no dose at all might be appropriate as opposed to an adjusted dose.

In the Panel's view, the claim implied that Eliquis could be used in all patients with VTE and without dose adjustment regardless of their renal function which was not so. This implication was compounded by the heading, prominent by virtue of its emboldened blue font. In the Panel's view, the claim 'Eliquis can be used in a broad range of patients with VTE with no dose adjustments regardless of age, weight or renal function*', in conjunction with the heading 'No dose adjustment' was misleading. Material had to be capable of standing alone and could not rely on qualification in a footnote etc to ensure Code compliance. Noting its comments above about how the claim might be seen by the reader, in the Panel's view, it was not sufficient to rely on the footnote below to qualify the strong and unequivocal claim. On balance, a breach was ruled. The Panel noted that the misleading claim in conjunction with the heading was incapable of substantiation and a further breach was ruled. Upon appeal, the Appeal Board did not consider that it was acceptable to rely on the qualifying text/footnote below to qualify the strong and unequivocal claim. The material was not sufficiently clear. The Appeal Board further considered that the misleading claim in conjunction with the heading was incapable of substantiation. The Panel's rulings were upheld.

In the Panel's view, the misleading claim did not encourage the rational use of the medicine and it considered that the Alliance had failed to maintain high standards and a breach was ruled. This ruling was upheld on appeal.

The Panel noted the unequivocal nature of the heading and claim and that information critical to patient safety had been relegated to a footnote. In the Panel's view, it was wholly inappropriate, in the particular circumstances of this case to place such critical information as a footnote to a more prominent claim and heading; some readers might not have seen the footnote or table of dosing considerations and as a result would not have considered subsequent relevant safety information. The Panel considered that patient safety was of the utmost importance and the Alliance's failures 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

A complainant who described himself/herself as a concerned UK health professional, complained about the promotion of Eliquis (apixaban) by Pfizer Limited and Bristol-Myers Squibb Pharmaceuticals Limited. The material at issue appeared on the Pulse website (Pulsetoday.co.uk). Eliquis was indicated, *inter alia*, for the prevention of stroke and other vascular emergencies in adults such as deep vein thrombosis (DVT) and pulmonary embolism (PE).

COMPLAINT

The complainant explained that he/she had received a promotional email with the subject heading 'Clot Busting – DVT/PE management at your fingertips [BMS/Pfizer Alliance funded content]'. There was nothing to indicate what medicine was at issue and there was no prescribing information in the email itself. The complainant clicked through to the linked webpage but noted that there was nothing on the webpage to prevent those who were not health professionals from seeing it.

The complainant also noted the claim that 'Eliquis can be used in a broad range of patients with venous thromboembolism (VTE) with no dose adjustments regardless of age, weight or renal function*'. The asterisk led to a statement which read 'Eliquis should be used with caution in patients with severe renal impairment (CrCl 15-29ml/min) for both the treatment of DVT/PE and prevention of recurrent DVT/PE. Eliquis is not recommended in patients with CrCl<15ml/min, or in patients undergoing dialysis'.

The complainant stated that thus, there clearly were dose adjustments.

The complainant stated that he/she recalled that a previous Eliquis advertisement failed to mention patients with lower eGFR. The complainant accepted that there was clarification in smaller text but given that most readers would not focus on the detail, the header of 'no dose adjustments' would be the main message for many doctors which was a patient safety issue. There were also many other contraindications listed in the summary of product characteristics (SPC) which were not mentioned in the 'broad range of patients.' This was also a patient safety issue as this information was misleading. The complainant noted that the advertisement was aimed at GPs who were not specialists in the product.

When writing to Pfizer and Bristol-Myers Squibb, the Authority asked them to consider the requirements of Clauses 4.1, 7.2, 7.3, 7.4, 9.1 and 2 of the Code.

RESPONSE

Bristol-Myers Squibb responded on behalf of the Bristol-Myers Squibb/Pfizer Alliance (the Alliance) and explained that the licensed indications of Eliquis included:

- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (see Section 4.4 for haemodynamically unstable PE patients).
- 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 mellitus; symptomatic heart failure (NYHA Class ≥ II).

The Alliance further explained that Pulse (Pulsetoday.co.uk) was an independent website intended for primary care, including GPs. Registration was also open to other primary care health professionals, including nurses and pharmacists. Pulse aimed to provide up-to-date information to health professionals, supporting them in treating patients more effectively.

The content on the Pulse website in question, referred to promotional educational content sponsored and funded by the Alliance, for venous thromboembolism (VTE) and took the form of a collection of VTE webpages, intended for UK health professionals.

Pulse held a list of health professionals who had consented and opted-in to receive third party communications, which included promotional content from pharmaceutical companies (health professional consent provided).

The email was classified and approved as promotional, and included a link directing recipients to the Alliance's promotional VTE webpages on the Pulse website. These webpages contained therapy area and management content in an area the Alliance had a product with a marketing authorisation and additionally included a section on the product itself.

The Alliance advocated transparency in all of its communications with health professionals. The subject line of the email clearly stated that the content was sponsored by the Alliance by the inclusion of the statement: 'BMS/Pfizer Alliance funded content'.

Additionally, the Alliance's involvement, the promotional nature of the email and the intended audience, were all made clear within the body of the email; this information was positioned at the very top of the email and read:

'This email contains promotional content that has been developed and funded by the Bristol-Myers Squibb / Pfizer Alliance and is intended for UK Healthcare Professionals. This email has been sent to you as you have opted in to receiving third-party information from Pulse.'

Beneath that statement was the heading 'Supporting information for successful DVT/PE management' and directly below this were the prominent logos of both companies. The email contained a brief overview on the number of people affected by VTE in the UK. The email was sent by Pulse on behalf of the Alliance to health professionals who had signed up to the Pulse platform and opted-in to receive such third-party emails. The final certified email and signatory qualifications were provided.

The Alliance recognised the importance of Clause 4.1 of the Code, that 'Prescribing information must be provided in a clear and legible manner in promotional material for a medicine'. However, given that the email did not discuss or indirectly refer to any medicine, the Alliance strongly believed that prescribing information did not need to be included and it refuted a breach of Clause 4.1. Prescribing information was available in the promotional Alliance sponsored VTE webpages on the Pulse website where specific reference was made to Eliquis.

As previously stated, the Alliance sponsored VTE webpages were developed to provide relevant educational content and resources for primary care health professionals to support their role in managing VTE. The intended audience, promotional nature and the Alliance's involvement was clearly stated at the outset of all of the webpages.

These Alliance sponsored webpages were built with five main sections: Home, Managing VTE, Preventing Recurrence, VTE Treatments and Eliquis in VTE. An additional 'Resources' section had also been provided.

The Alliance noted that the PMCPA had informed the complainant that it did not believe there had been a breach of Clause 28.4 of the Code, with which the Alliance was aligned, as the webpages at issue were contained within a relevant independently produced electronic journal intended for health professionals or other relevant decision makers.

The allegation regarding 'no dosing adjustments' related to the section entitled 'Eliquis in VTE'. The section covered information on the Eliquis dosing regimen required for all patients receiving treatment of acute VTE, using a visual to show the initiation dose (10mg BD), the treatment dose (5mg BD), and if indicated, the extended therapy dose (2.5mg BD). The frequency of twice daily dosing was clearly described as per Section 4.2 of the Eliquis SPC.

With regard to dose reduction in VTE patients, Section 4.2 of the SPC contained the following text:

- *Body weight*
  VTEt – No dose adjustment required (see sections 4.4 and 5.2).
- *Gender*
  No dose adjustment required (see section 5.2).
- *Elderly*
  VTEt – No dose adjustment required (see sections 4.4 and 5.2).
- *Renal impairment*
  In patients with mild or moderate renal impairment, the following recommendations apply:
  - For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt), no dose adjustment is necessary (see section 5.2).'

In patients with severe renal impairment (creatinine clearance 15-29ml/min) the following recommendations applied (see Sections 4.4 and 5.2):

> 'For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt) apixaban is to be used with caution; [The Alliance noted that 'use with caution' was not the same as a dose adjustment.]'

In patients with creatinine clearance <15 ml/min, or in patients undergoing dialysis, there was no clinical experience therefore apixaban was not recommended (see Sections 4.4 and 5.2). [The Alliance noted that 'not recommended' was not the same as a dose adjustment.]

Management of VTE was different to that of NVAF. Treatment of NVAF had specific criteria for dose reduction as detailed in Section 4.2 of the SPC:

> '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).

The Alliance believed it was important that prescribers were clear about the distinction between the dose reduction required for treatment of NVAF vs VTE patients where dose reduction was not required, as per the SPC. The Alliance therefore did not consider that the title 'no dose adjustment' was misleading. Beneath this title, the Alliance included dosing recommendations for Eliquis to be used with caution in severe renal impairment, and that Eliquis was not recommended in renal failure and patients undergoing dialysis. This information was placed here for completeness and clarity; these recommendations did not equate to dose adjustments for these patients. The complainant also referred to the 'smaller text' in this paragraph, which the Alliance deemed to be suitable, legible, and clear.

As Eliquis was a treatment option for VTE management, each webpage contained a clear and prominent direct, single click link to the Eliquis prescribing information, enabling health professionals to fully appreciate how the prescribing information related to any information and claims made within the webpage. A factual overview of the dosing considerations had been provided on the same webpage. Within the 'No dose adjustments' subsection, a clear, concise table summarised the dosing considerations of the four non-vitamin K antagonist oral anticoagulants (NOACs) by age, weight and renal function. The NOACs were categorised according to their therapeutic class and the data within this table was both factual and accurate, and in line with the respective SPCs. The SPC for each NOAC was clearly referenced and hyperlinked at the bottom of the webpage. There were no contraindications related to age and weight of VTE patients for Eliquis, therefore the Alliance believed Eliquis could be prescribed in a broad range of patients. The Alliance believed the webpage was sufficiently complete to allow health professionals to form their own opinion of the therapeutic value of Eliquis. The Alliance believed that the webpages, and specifically the section in question, were consistent with the licence and requirements of Clauses 7.2, 7.3 and 7.4 of the Code, and it thus denied any breaches of those clauses.

The Alliance did not believe that the content of the Alliance sponsored VTE webpages was misleading. The Alliance stated that it operated to high standards, appreciating the special nature of pharmaceuticals and its dedication to its patients; it denied a breach of Clause 9.1.

The Alliance stated that it was fully committed to compliance with the Code and denied any breach of Clause 2. The Alliance strongly believed that the content of the email and the Alliance sponsored VTE webpages were clear in intent, accurate and not misleading and did not compromise patient safety. Therefore, the Alliance did not believe it had undermined confidence in the industry.

The Alliance stated that it had come to its attention that the email sent out by Pulse was an earlier version of the material and not the final certified version provided by the Alliance. The email sent by Pulse differed from the final certified form with regard to the subject line and the date of preparation only; the content was the same as the certified version. The Alliance was confident that the content of the email that was distributed was not inaccurate or misleading. The Alliance referred to the final version of the email sent by Pulse to Bristol-Myers Squibb for final form certification and the final certified email (PDF) with its certificate. The Alliance provided a copy of the email correspondence between its creative agency and Pulse confirming the necessary amends in the email had been implemented for certification.

The Alliance detailed actions taken by the parties to ensure that the error did not happen again. Pulse had confirmed that all previous versions of the email had been removed from its platform, and hence no further distribution of the incorrect email to any health professionals was possible (copy provided).

PANEL RULING

The Panel noted that the email received by the complainant with the subject line 'Clot Busting – DVT/PE management at your fingertips [BMS/Pfizer Alliance funded content]' was, according to the Alliance, not the final certified version provided to Pulse by the Alliance. The Panel noted the Alliance's submission that the email sent by Pulse differed from the final certified form with regard to the subject line and the date of preparation only; the content was the same as the

certified version. The Panel noted that this was not the subject matter of the complaint and thus the Panel made no ruling on this point.

The Panel considered that the Alliance's submission that the email was classified and approved as promotional, and included a link directing recipients to the promotional Alliance sponsored VTE webpages on the Pulse website, was inconsistent with its submission that given the email did not discuss or indirectly refer to any medicine, prescribing information did not need to be included, and prescribing information was available in the linked promotional Alliance sponsored VTE webpages on the Pulse website where specific reference was made to Eliquis. The Panel considered that this approach demonstrated a fundamental misunderstanding of the Code. The Panel noted the broad definition of promotion at Clause 1.2 and that it was an accepted principle under the Code that a product could be promoted without its name ever being mentioned. Prescribing information had to be provided in all promotional material.

The Panel noted that the subject line of the email received by the complainant included the claim 'Clot busting' and the email referred to DVT/PE management, anticoagulation treatment and the BMS/Pfizer Alliance which marketed Eliquis, an anticoagulant used for, *inter alia*, the treatment of DVT/PE. Noting the broad definition of promotion at Clause 1.2, the Panel considered that the email was promotional. In that regard, the Panel noted that at the outset of the email was a prominent statement which read 'This email contains promotional content that has been developed and funded by the Bristol-Myers Squibb / Pfizer Alliance ….'. In the Panel's view, given that readers might not click through to the Pulse website, the email should be capable of standing alone with regard to the requirements of the Code and therefore should have included prescribing information or a clear and prominent statement as to where prescribing information could be found by way of a clear and prominent direct single click. The Panel ruled a breach of Clause 4.1 in relation to the email and the failure to provide Eliquis prescribing information. This ruling was appealed.

The Panel noted that in the screenshot provided by the complainant the claim 'Eliquis can be used in a broad range of patients with VTE with no dose adjustments regardless of age, weight or renal function*' appeared in the section of the website entitled 'Eliquis in VTE' below the emboldened heading in dark blue font 'No dose adjustments'. The asterisk led the reader to a statement immediately beneath in smaller italic font which read 'Eliquis should be used with caution in patients with severe renal impairment (CrCl 15-29ml/min) for both the treatment of DVT/PE and prevention of recurrent DVT/PE. Eliquis is not recommended in patients with CrCl<15ml/min, or in patients undergoing dialysis'. The Panel noted that following this was a table which summarised the dosing considerations of the four non-vitamin K antagonist oral anticoagulants (NOACs) by age, weight and renal function. The Panel noted that the companies had been provided with a copy of the anonymised complaint and screenshot. The relative font size in the version printed by the case preparation manager and also provided to the companies was different. The Panel made its ruling based on the version provided by the complainant which appeared to be consistent with that provided by the companies as part of their response.

The Panel noted the layout of the relevant webpages provided by the Alliance which were, in the Panel's view, designed to be viewed digitally. The Panel queried how the information would be viewed on different devices and if the text within the table would be legible across different platforms/devices particularly a mobile phone. It appeared to the Panel that the site made use of infinite scrolling which was a web-design technique that loaded content continuously as the user scrolled down the page, eliminating the need for pagination. In the Panel's view, it was not

unreasonable to assume that some readers might have read the claim at issue without scrolling down further to see the footnote or table, or scroll directly past the footnote and table particularly noting that it appeared from the headline and claim at issue that Eliquis could be used in a broad range of patients with VTE and there were no dosage adjustments or concerns with regards to patients with impaired renal function.

The Panel noted that Section 4.2 of the Eliquis SPC stated that for VTEt no dose adjustment was required for body weight, gender or the elderly. The Panel noted that Section 4.2 stated under the heading 'Renal impairment' that for the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt): in patients with mild or moderate renal impairment no dose adjustment was necessary; in patients with severe renal impairment (creatinine clearance 15-29ml/min) apixaban was to be used with caution; and in patients with creatinine clearance <15 ml/min, or in patients undergoing dialysis, there was no clinical experience therefore apixaban was not recommended.

The Panel noted the Alliance's submission that there were no contraindications related to the age and weight of VTE patients for Eliquis therefore, in its view, Eliquis could be prescribed in a broad range of patients. The Panel disagreed with the Alliance's submission that the recommendations for patients with severe renal impairment (creatinine clearance 15-29ml/min) and in patients with creatinine clearance <15 ml/min, or in patients undergoing dialysis did not equate to dose adjustments and therefore the claim at issue was not misleading. The Panel noted that these recommendations were included in Section 4.2 of the SPC which dealt with posology and method of administration and were included in the table referred to above which summarised the dosing considerations of the four NOACs by age, weight and renal function. In the Panel's view, the recommendations therefore would be considered within the context of dose adjustments. In the Panel's view, the fact that a medicine should only be used with caution or not be used at all in patients with VTE and certain levels of renal impairment was relevant and important information; it might mean that no dose at all might be appropriate as opposed to an adjusted dose.

In the Panel's view, the claim implied that Eliquis could be used in all patients with VTE and without dose adjustment regardless of their renal function which was not so. This implication was compounded by the heading, prominent by virtue of its emboldened blue font. In the Panel's view, the claim 'Eliquis can be used in a broad range of patients with VTE with no dose adjustments regardless of age, weight or renal function*', in conjunction with the heading 'No dose adjustment' was misleading. Material had to be capable of standing alone with regard to the requirements of the Code and could not rely on qualification in a footnote etc to ensure Code compliance. Noting its comments above about how the claim might be seen by the reader, in the Panel's view, it was not sufficient to rely on the footnote below to qualify the strong and unequivocal claim. On balance, a breach of Clause 7.2 was ruled. The Panel noted that the misleading claim in conjunction with the heading was incapable of substantiation and a breach of Clause 7.4 was ruled. These rulings were appealed.

The Panel noted that Clause 7.3 was raised by the case preparation manager. The Panel did not consider that the complainant had made an allegation with regard to Clause 7.3 and therefore made no ruling.

In the Panel's view, the misleading claim did not encourage the rational use of the medicine and it considered that the Alliance had failed to maintain high standards and a breach of Clause 9.1 was ruled. This ruling was appealed.

The Panel noted the unequivocal nature of the heading and claim in question which had been ruled in breach of the Code above. The Panel considered that the information relegated to the footnote was important and critical to patient safety. In the Panel's view, it was wholly inappropriate, in the particular circumstances of this case to place such critical information as a footnote to a more prominent claim and heading which implied that the reader did not need to be concerned about dose adjustment and renal impairment. Some readers might have absorbed that unequivocal initial message and either consequently decided not to consider subsequent information having been incorrectly reassured about dose adjustment and renal impairment or simply not seen the footnote or table and as a result would not have considered subsequent relevant safety information. The Panel noted that Section 4.2 of the SPC referred to an increased bleeding risk in patients with severe renal impairment. The Panel considered that patient safety was of the utmost importance and the Alliance's failures in this regard brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled. This ruling was appealed.

* * * * *

During its consideration of this case, the Panel was concerned to note that a non-certified version of the email had been sent by Pulse on the Alliance's behalf. The Panel noted the Alliance's submission in this regard that Pulse had been notified of its error and the Alliance was currently working collaboratively to identify mechanisms to avoid this occurring again. The Panel noted that even in the absence of the 'Clot busting' claim in its view the email was promotional and therefore its rulings would have similarly applied to the certified email had it been the subject of the complaint.

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APPEAL BY THE ALLIANCE

Clause 4.1

The Alliance acknowledged that the broad definition of promotion set out in Clause 1.2 of the Code included 'any activity undertaken by a pharmaceutical company or with its authority which promotes the administration, consumption, prescription, purchase, recommendation, sale, supply or use of its medicine'. In this regard the Alliance agreed that the intention of directing health professionals to the Alliance sponsored VTE webpages on the Pulse website was to promote the appropriate use of Eliquis in VTE management. The Alliance considered that the entire initiative was promotional in nature and so it certified all materials, including the email in question, accordingly, in line with the requirements of Clause 14.1 of the Code. The statements:

> 'This email contains promotional content that has been developed and funded by the Bristol-Myers Squibb / Pfizer Alliance and is intended for UK Healthcare Professionals…...'
>
> and
>
> 'To visit the VTE management microsite, click here. The site contains promotional content and is intended for UK healthcare professionals only.'

were included in the email to ensure that recipients were clear that the email related to a promotional activity but did not suggest that the Alliance considered the email itself promoted a specific medicine. The Alliance submitted that it ensured that all requirements of Clause 4 were met in the promotional Alliance sponsored VTE webpages on the Pulse website where specific reference was made to Eliquis with the intention of encouraging its appropriate use.

The Alliance understood that it was possible to promote a medicine without referring to that medicine but disagreed with the Panel's assessment that the email sent by Pulse itself promoted the use of Eliquis. There were no direct or indirect references or claims related to Eliquis. The email did not therefore meet the definition of '*promotional material* **for a medicine**' described in Clause 4.1 of the Code and inclusion of prescribing information was therefore not required.

The Alliance submitted that the Panel's conclusion that the email, irrespective of the subject line, promoted Eliquis and required prescribing information seemed to be inconsistent with previous rulings upon which the Alliance had built its approach. Case AUTH/2931/1/17 and Case AUTH/2941/2/17 both addressed the same issue in relation to invitations to promotional meetings, and in both cases the Panel concluded that whilst it might be prudent to provide prescribing information with the invitations, as the invitations did not promote any specific company medicines it was not a breach of the Code not to do so. In both of these cases the invitations clearly identified a pharmaceutical company, a therapy area and included reference to speakers covering treatment strategies. The Alliance was unable to identify how those invitations differed from the email in question.

The Alliance submitted that that the email did not require prescribing information and it therefore appealed the Panel's ruling of a breach of Clause 4.1.

Clauses 7.2, 7.4, 9.1 and 2 - background Information

The Alliance noted that Eliquis was licensed for the treatment and prevention of recurrent VTE and prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF). The dosing regimens for the two indications (VTE and NVAF) were very different and the incorrect dosing of NOACs represented a serious patient safety concern.

The Alliance submitted that the target audience for the VTE webpages was primary care health professionals to support their role in the diagnosis, treatment and long-term care of patients with VTE. The Alliance recognised that primary care health professionals had greater experience in prescribing Eliquis in patients with NVAF. The entire promotional Pulse website was about VTE as was evident from the wireframe and name on the tabs. One objective of the webpages was to ensure understanding of the distinct dosing recommendations in the VTE population.

Table 1. Use of Eliquis in patients with renal impairment

Renal Impairment	Patients with NVAF	Patients with VTE
Mild or moderate	Dose reduction ONLY necessary if serum creatinine ≥1.5 mg/dl AND patient was either ≥80 years OR ≤60 kg	No dose adjustment was necessary *(see section 5.2 of SPC)*

Severe: (creatinine clearance 15-29 ml/min)	Dose reduction necessary	Use with caution *(see sections 4.4 and 5.2 of SPC)*
On dialysis or renal failure: (creatinine clearance < 15 ml/min)	Not recommended	Not recommended *(see sections 4.4 and 5.2 of SPC)*

The Alliance noted that the Panel ruled that the use of Eliquis in VTE patients with severe renal impairment and renal failure, fell under the scope of 'dose adjustments' because they were all found in the same section of the SPC. The Panel's apparent position was that if the medicine could not be used at all in certain patient populations then this was categorised as a dose reduction. From Table 1 above and from both regulatory and clinical perspectives, it was clear that there was no requirement to adjust the dose of Eliquis in VTE patients with renal impairment.

The Alliance submitted that therefore, on this VTE website, it was true to say that for Eliquis in VTE, there were no dose adjustments required and the heading accurately reflected this.

The Alliance submitted that the claim below stood alone because it was substantiated by the SPC and provided a clear clinical interpretation for the reader. As per Table 1 above, in VTE, Eliquis could be used with no dose adjustments regardless of age, weight or renal function.

Layout and flow of webpages

The Alliance submitted that that the claim and associated cautions with regard to renal impairment, were preceded by a clear and prominent schematic and video which not only detailed the licensed dosing criteria but also highlighted the cautions relating to the use of Eliquis in patients with severe renal impairment and in patients with creatinine clearance < 15ml/min or in patients undergoing dialysis. The layout of the webpage was such that it was impossible for readers to navigate to the claim and table in question without first seeing this information. In the unlikely event that readers missed this information directly under the claim, they would have already received this information at least once and potentially twice if they had chosen to view the video.

Inclusion and prominence of relevant information

The Alliance submitted that the following information was prominently displayed directly underneath the claim and preceded the table in question.

> '* Eliquis should be used with caution in patients with severe renal impairment (CrCl 15–29ml/min) for both the treatment of DVT / PE and prevention of recurrent DVT / PE. Eliquis is not recommended in patients with CrCl <15ml/min, or in patients undergoing dialysis.'

Although the Panel called additional information a 'footnote', the Alliance submitted that this was further information presented directly after the claim – it was not separately presented, as genuine footnotes often were, at the end of the webpage.

The Alliance submitted that this information was directly under the claim and included for completeness and clarity to remind readers that the SPC required caution in severe renal impairment and was not recommended in renal failure or dialysis. This information was not required to qualify the claim which was about dose adjustments. Therefore, even on the narrow grounds that it was missed by readers, the heading and claim still stood alone.

The Alliance submitted that the table at issue made it clear through its size and the use of colour, how the product might be used in patients with renal impairment.

The Alliance noted that the Panel ruled that it was 'not unreasonable to assume' that a reader might scroll down and read the heading and claim without seeing the information or the table (image below). The Alliance submitted that this was not a reasonable assumption and the Alliance submitted that:

- the information was not a footnote; it was not required to qualify the heading or the claim about dose adjustment, but merely to provide further information on renal function
- neither the size nor the use of colour within the table were considered by the Panel and would be very hard for a reader to miss
- the heading, claim, information and table would have been clearly seen together in one view by the reader
- the overall impression was therefore not misleading.

The Alliance submitted that the table and statement below the heading were prominent and provided holistic information; and there was no evidence to support the view that prescribers would miss such clearly placed information.

Summary

The Alliance submitted that it appealed the Panel's rulings of breaches of:

- Clause 4.1 because the email did not require inclusion of Eliquis prescribing information
- Clause 7.4 because the heading was capable of substantiation
- Clause 7.2 because the claim was not misleading
- Clause 9.1 because the claim did not discourage the rational use of the medicine and high standards were met at all times
- Clause 2 because all the relevant information was present and patient safety had not been compromised

COMMENTS FROM THE COMPLAINANT

The complainant acknowledged receipt of the appeal and stated that he/she was sure that the Appeal Board was best placed to review the case.

APPEAL BOARD RULING

The Appeal Board noted the Alliance's submission that the subject line of the email at issue which was received by the complainant was different to that certified although the content was otherwise the same. The company representatives at the appeal noted that, when the email in question was sent, the Alliance did not have a mechanism to check prior to its despatch whether the email in question was the same as that certified. The Appeal Board noted that the Alliance had been let down by its publisher and the complainant had received the email in question with the unapproved subject line 'Clot Busting – DVT/PE Management at your fingertips [BMS/Pfizer Alliance funded content]'. The Appeal Board considered that the statement 'Clot Busting' next to the indication 'DVT/PE Management' and the company 'BMS/Pfizer Alliance' amounted to the indirect promotion of a medicine. The Alliance had one medicine in this area, Eliquis.

The Appeal Board noted that the email at issue had been certified by the Alliance as promotional material and the email stated at the outset 'This email contains promotional material…'. The Appeal Board noted that the representatives from the Alliance at the appeal stated that the email had been certified as promotional because the wider project was promotional but that the email in isolation was non-promotional. In addition, the company representatives at the appeal stated that this classification was easier due to internal audit purposes, the Appeal Board queried the rationale of such an approach but noted that this was not relevant to the appeal.

The Appeal Board noted that the email in question contained a link to a promotional website and its sole purpose was to direct the recipient to that website. The link was thus an integral part of the email. It was noted at the appeal that health professionals could also search for and find the webpages at issue on the main Pulse website. The Appeal Board noted that the Alliance appeal cited two cases (Case AUTH/2931/1/17 and Case AUTH/2941/2/17) in support of its position that the email in question could be considered in isolation and did not require prescribing information. The Appeal Board noted that both these cases completed at the Panel level, neither had been appealed and as such did not bind the Appeal Board. In any event the Appeal Board noted that the cases cited were factually different to that presently before the Appeal Board and were thereby distinguishable. The Appeal Board also noted that the Panel in those cases had considered that the invitations did not promote any specific medicines and the Panel had stated that whilst it was not in breach of Clause 4.1 to omit prescribing information it would have been prudent to include it in the invitations at issue. In any event the Appeal Board noted that each case was considered on its own individual merits.

In conclusion the Appeal Board considered that the email in question was promotional and in any event was inextricably linked to the promotional webpages irrespective of the incorrect subject heading to the email. The Appeal Board consequently upheld the Panel's ruling of a breach of Clause 4.1. The appeal on this point was unsuccessful.

The Appeal Board noted from the screen shot provided by the complainant that the heading in dark blue font 'No dose adjustments' was immediately followed by the claim 'Eliquis can be used in a broad range of patients with VTE with no dose adjustments regardless of age, weight or renal function*' which appeared in the section of the website entitled 'Eliquis in VTE'. The asterisk referred to a statement immediately beneath in smaller italic font which read 'Eliquis should be used with caution in patients with severe renal impairment (CrCl 15-29ml/min) for both the treatment of DVT/PE and prevention of recurrent DVT/PE. Eliquis is not recommended in patients with CrCl<15ml/min, or in patients undergoing dialysis'. The Appeal Board noted that the claim was followed by a table which summarised the dosing considerations of the four non-vitamin K antagonist oral anticoagulants (NOACs) by age, weight and renal function.

The Appeal Board noted that Section 4.2 of the Eliquis SPC stated that under the heading 'Renal impairment' that for the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt): in patients with mild or moderate renal impairment no dose adjustment was necessary; in patients with severe renal impairment (creatinine clearance 15-29ml/min) apixaban was to be used with caution; and in patients with creatinine clearance <15ml/min, or in patients undergoing dialysis, there was no clinical experience therefore apixaban was not recommended. The Appeal Board noted the submission of the companies' representatives at the appeal about what they considered to be the differences between a dose adjustment and a reference in the SPC that Eliquis be used with caution or that it was not recommended. The Appeal Board did not consider that the matter was as straightforward as implied by the companies' representatives.

The Appeal Board noted that whilst the companies referred to the relevant material appearing in a page format, the material at issue scrolled continuously and it was concerned that a health professional could scroll through the material and stop at the bold claims 'No dose adjustments' and 'Eliquis can be used in a broad range of patients with VTE with no dose adjustments regardless of age, weight or renal function*' without either scrolling down further to see the qualifying text/footnote or table, or scrolling directly past the qualifying text/footnote and table. The Appeal Board's concern was compounded by the fact that the initial impression from these prominent headline claims was that Eliquis could be used in a broad range of patients with VTE and there were no dosage adjustments or concerns with regards to patients with impaired renal function. In that regard the Appeal Board was particularly concerned about the use of the term 'regardless' in the claim 'Eliquis can be used in a broad range of patients with VTE with no dose adjustments regardless of age, weight or renal function*'. The Appeal Board considered that if a medicine should only be used with caution or not at all in patients with VTE and certain levels of renal impairment this was relevant and important information; it might mean that no dose at all might be appropriate.

The Appeal Board noted the Alliance representatives' submission that GPs would be more familiar with the use of Eliquis for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and the need for dose reduction in relation to two or more of the age, body weight and serum creatinine criteria. The Alliance submitted there was a risk that GPs would use similar dose reductions when prescribing for VTE and this was not necessary.

The Appeal Board considered that the claim 'Eliquis can be used in a broad range of patients with VTE with no dose adjustments regardless of age, weight or renal function' was misleading. As stated above the Appeal Board was particularly concerned about the use of the word 'regardless' as Section 4.2 of the Eliquis SPC was clear Eliquis could not be prescribed 'regardless' of renal function. This implication was compounded by the emboldened prominent blue heading. The Appeal Board considered that there was sufficient confusion such that a health professional might inappropriately consider giving Eliquis to patients with end stage renal failure. Material had to be capable of standing alone with regard to the requirements of the Code and could not rely on qualification in a footnote etc to ensure Code compliance. Noting its comments above the Appeal Board did not consider that it was acceptable to rely on the qualifying text/footnote below to qualify the strong and unequivocal claim. The material was not sufficiently clear. The Appeal Board therefore upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful. The Appeal Board considered that the misleading claim in conjunction with the heading was incapable of substantiation. The Appeal Board therefore upheld the Panel's ruling of a breach of Clause 7.4. The appeal on this point was unsuccessful.

In the Appeal Board's view, the material did not encourage the rational use of the medicine and it considered that the Alliance had failed to maintain high standards. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

The Appeal Board noted its rulings above, and the unequivocal nature of the heading and claim in question with critical information relevant to patient safety being relegated to the smaller text below. Both under- and overdosing of Eliquis had critically important patient safety outcomes. In the particular circumstances of this case the placing of such important patient safety information below the claim 'Eliquis can be used in a broad range of patients with VTE with no dose adjustments regardless of age, weight or renal function*' and heading 'No dose adjustments' implied that the reader need not be concerned about dose adjustment and renal impairment. The Appeal Board noted that Section 4.2 of the SPC referred to an increased bleeding risk in patients with severe renal impairment. The Appeal Board considered that patient safety was of the utmost importance and the Alliance's failures 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. The appeal on this point was unsuccessful.

Complaint received **27 September 2019**

Case completed **13 May 2020**