CASES AUTH/3595/1/22 and AUTH/3596/1/22

COMPLAINANT v BRISTOL MYERS SQUIBB AND PFIZER

Concerns about Eliquis Website

CASE SUMMARY

This case was in relation to four patient information booklets on the Bristol Myers-Squibb and Pfizer Eliquis (apixaban) website which were not updated following updates to the Eliquis Summary of Product Characteristics (SPC).

The Panel ruled a breach of the following Clause(s) of the 2021 Code in relation to each of the four booklets for failing to include certain information following updates to the SPC which meant that the booklets were inaccurate or misleading:

Breach of Clause 6.1	**Including misleading and inaccurate information**
Breach of Clause 5.1	**Failing to maintain high standards**

The Panel ruled no breach of the following Clause(s) of the 2021 Code in relation to each of the four booklets as in its view failure to include certain information following updates to the SPC did not mean that the booklets were inaccurate or not up-to-date as alleged and the Panel did not consider that the complainant had established that patient safety had been prejudiced:

No Breach of Clause 6.1	**Requirement that information must be accurate, up-to-date and not misleading**
No Breach of Clause 2	**Requirement that activities or material must not bring discredit upon, or reduce confidence in, the pharmaceutical industry**

This summary is not intended to be read in isolation.

For full details, please see the full case report below.

FULL CASE REPORT

A contactable complainant who stated that he/she was a GP was concerned about material on the Bristol Myers-Squibb and Pfizer Eliquis (apixaban) website.

Eliquis was indicated for the prevention of venous thromboembolic events (VTE) in adult patients who had undergone elective hip or knee replacement surgery and the prevention of stroke and systemic embolism in adult patients 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) and the

treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

COMPLAINT

The complainant alleged that the patient materials section on the Eliquis website was not fit for purpose. The patient material information booklets did not contain the latest information as per the Eliquis summary of product characteristics (SPC). The complainant stated that the SPC had been updated numerous times since the patient material was created in April 2019. The complainant stated that this was a serious safety concern to him/her as patients were being provided incorrect, inaccurate information which was not up-to-date. The complainant stated that this was unacceptable and proved that all these pharmaceutical companies cared about was profits over patient safety. The complainant stated that companies could not even be 'bothered' to keep their patient material up-to-date.

The complainant referred to four separate patient information booklets on the website (https://www.eliquis.co.uk/hcp/overview-patient-material) including: Patient Information Booklet for adult patients prescribed ELIQUIS for stroke prevention in NVAF; Patient Information Booklet for patients switching from warfarin to ELIQUIS for stroke prevention in NVAF; Patient Information Booklet for patients on ELIQUIS for treatment of DVT / PE or prevention of recurrent DVT / PE in adults; and Patient Information Booklet for adult patients on ELIQUIS for prevention of VTE after elective hip or knee replacement surgery. The complainant stated that the four patient information booklets were in many languages, equating to over 20 patient booklets dated April 2019.

When writing to Bristol Myers Squibb and Pfizer, the Authority asked the companies to consider the requirements of Clauses 5.1, 6.1 and 2 of the 2021 Code.

RESPONSE

Bristol Myers-Squibb responded on behalf of the Bristol Myers Squibb and Pfizer Alliance as the patient booklets were certified by Bristol Myers Squibb.

Background

The Alliance stated that it was committed to supporting patients who had been prescribed Eliquis (apixaban) with up-to-date, accurate and balanced information through a variety of different resources including a patient website, the patient information leaflet (PIL) and patient booklets.

The PIL was a comprehensive resource for patients who had been assessed as suitable to be prescribed apixaban by a health professional. The patient booklets were supplementary resources for patients who had already been prescribed apixaban. The booklets were not intended to replace the PIL and throughout each booklet the reader was encouraged to read and reference the PIL as well. As a regulatory requirement all patients were provided with the PIL within their prescribed medication packaging.

The Alliance refuted the allegation that all four patient booklets were out-of-date and inaccurate at the time of the complaint.

The four booklets in question listed below were referred to as such in the companies' response:

- **Booklet One** – Helping prevent stroke caused by non-valvular atrial fibrillation. Mercury Job Code 432UK1900396-01. Date of preparation: April 2019. Veeva PromoMats job code: 432-GB-2100443.

- **Booklet Two** – Switching from Warfarin to Eliquis (apixaban) patient information booklet. Mercury Job Code: 432UK1900396-02. Date of preparation: April 2019. Veeva PromoMats job code: 432-GB-2100450.

- **Booklet Three** – Helping to treat deep vein thrombosis and pulmonary embolism and helping prevent recurrence. Mercury Job Code: 432UK1900396-03. Date of preparation: April 2019. Veeva PromoMats job code: 432-GB-2100451.

- **Booklet Four** – Helping prevent blood clots after hip and knee replacement surgery). Veeva PromoMats job code: 432-GB-2100641. Date of preparation: July 2021.

The Alliance stated that Booklets 1, 2 and 3 had a date of preparation of April 2019, were certified in June 2019 and were subsequently made accessible in the appropriate sections of the Eliquis website. In compliance with the Code, all 3 booklets were recertified without changes on the 10 June 2021, prior to their expiry.

The initial approvals of these materials were via a previously used electronic approval system (EAS). All BMS materials had since been migrated into the new EAS, Veeva PromoMats. Therefore, the original approval certificates differed from the recertification confirmations.

A copy was requested of Booklet 4 which had a date of preparation of April 2019. The previous approved version of Booklet 4 had a date of preparation of February 2018 and was withdrawn prior to its expiry. Once updated, it was reapproved with a new job bag number and a date of preparation of July 2021 within Veeva PromoMats. Hence, the 2019 version of this booklet did not exist. The Alliance believed that the complainant was mistaken and the version that they would have seen on the website had a date of preparation of July 2021. This booklet was therefore still valid, up-to-date and accurate.

Details of the updates to the SPC and PIL since April 2019 were provided by the Alliance.

The Alliance stated that the intention of the patient booklets was to provide patients who had already been prescribed apixaban with relevant and easily digestible information about their condition and treatment in a patient friendly format using appropriate language. The patient booklets were not intended to replace the comprehensive PIL, which was provided to all patients within their medication packaging. No patient would receive a patient booklet without receiving the PIL. The patient booklets signposted patients to the PIL on numerous occasions to access the full information on apixaban. Booklet 1 referenced the PIL eight times, Booklet 2 referenced the PIL seven times. Booklet 3 referenced the PIL six times. Booklet 4 referenced the PIL eight times. Prior to downloading the patient booklets from the website, the health professionals were advised that the booklet was not intended to replace the PIL.

The Alliance believed that it was important to consider the intended reader when forming communication and further, that the information provided was appropriate and conferred respect and trust in the audience. It was crucial for patients to be provided with clear, concise, and

relevant information that they could navigate easily without feeling overwhelmed and without receiving multiple forms of duplicated information.

The Alliance submitted that for all SPC and/or PIL updates, it undertook a robust review of active materials to determine whether any updates were required. A list of changes to the SPC and PIL from April 2019 was provided. All active materials were assessed and withdrawn or updated as appropriate. These changes were not incorporated into the patient booklets based on one or more of the following:

1 The following were considered to be detailed topics (antiphospholipid syndrome, catheter ablation, and reversal agent) which were deemed to be particularly relevant to the *prescriber*. Patients reading the booklets were referred to the PIL for these more detailed topics.
2 Only common and serious side effects were highlighted in the patient booklets. Patients were referred to the PIL for a comprehensive list which would include rare, uncommon or unknown frequency adverse medicine reactions such as Erythema multiforme and hair loss.
3 Related to language changes which did not alter the prescribing recommendations for apixaban.

The patient booklets were supplementary resources for patients who had already been prescribed apixaban. The booklets were not intended to replace the PIL and throughout each booklet the reader was referred to the PIL for further information.

Clause 6.1

The Alliance submitted that the patient booklets were accurate, fair, balanced and up-to-date. On the Eliquis Website, all patient booklets were within their expiry date and had been reviewed, assessed, and reapproved within the 2-year timeframe in accordance with the Code. At the time of the SPC and PIL updates, all active materials were assessed by the medical team. No updates were required to the patient booklets.

The Alliance therefore strongly refuted a breach of Clause 6.1.

Clause 5.1

The Alliance submitted that it had acted responsibly in providing patients with accurate, clear, concise, up- to-date and relevant supportive information in the form of patient-friendly booklets, alongside the comprehensive PIL that they were already provided with. The Alliance believed that it had maintained high standards by addressing the patient need and by considering the audience type when communicating. The Alliance aimed to confer respect and trust with the audience.

Considering the above, the Alliance strongly refuted a breach of Clause 5.1.

Clause 2

The Alliance strongly refuted this clause. The Alliance submitted that it took patient safety very seriously and was committed to ensuring that all materials were up-to-date, accurate, balanced and appropriate for the patient. The Alliance did not believe that patient safety had been

compromised. The Alliance prioritised and maintained patient safety at the core of all its activities.

The Alliance stated that it was committed to following the Code and took its responsibility to uphold the high standards very seriously.

PANEL RULING

The Panel noted that the complainant stated that the patient information booklets were created in April 2019 and alleged that the SPC had been updated numerous times since and the patient information booklets did not contain the latest information as per the Eliquis SPC. The complainant did not provide any specific details of which updated information he/she was concerned was not included within the booklets. Details of the updates to the SPC and PIL since April 2019 were, however, provided by the Alliance.

The Panel noted the Alliance's submission that Booklets one, two and three which all had a date of preparation of April 2019 were certified in June 2019 and recertified without changes on 10 June 2021 prior to their expiry. The Panel noted that the re-approval certificates provided by the Alliance contained different job numbers to the booklets available on the website at the time of the complaint. In this regard, the Panel noted the Alliance's submission that the original approval certificates differed from the recertification confirmations because the initial approvals were done using one electronic approval system (EAS) and had then been moved to and recertified in a different system.

The Panel noted the Alliance's submission that the previous approved version of Booklet four had a date of preparation of February 2018 and was withdrawn prior to its expiry. Once updated, it was reapproved with a new job bag number and a date of preparation of July 2021 within Veeva PromoMats and was the version the complainant would have seen on the website; an April 2019 version of this booklet did not exist.

The Panel noted that the version of Booklet one which was available to download from the Eliquis website at the time the complaint was submitted included the job number 432UK1900396-01 and April 2019 as the date of preparation which was according to the Alliance re-certified in June 2021 under the job code: 432-GB-2100443. Booklet one was a 36-page booklet titled 'Helping prevent stroke caused by non-valvular atrial fibrillation'. The booklet began by discussing what atrial fibrillation was, what caused it and what the signs and symptoms of a stroke were. It then went on to discuss anticoagulants to help prevent stroke in people with non-valvular atrial fibrillation and Eliquis. The Panel noted that the booklet included a section titled 'Things to be aware of when taking Eliquis (apixaban)' which included the importance of the patient carrying the patient alert card inside the pack and showing it to treating health professionals and informing such health professionals that they were taking Eliquis if having any surgical or dental procedures and about any other medicines that they were taking. It further stated that it was important that patients looked out for any signs of bleeding and that they should not take Eliquis if they were allergic to any of the ingredients, if they were bleeding excessively, or if they had (or were thought to have) a condition that increased the risk of serious bleeding, if they had liver disease leading to an increased risk of bleeding or if they were taking medicines to prevent blood clotting. It further stated that Eliquis was not recommended in other instances such as pregnancy, breast feeding, in patients with prosthetic heart valves (with and without atrial fibrillation), and in patients taking certain other medications and referred readers to the patient information leaflet for the full list. The section ended by

asking readers to please ensure that they read the patient information leaflet (inserted in the medicine packaging) thoroughly before taking the medicine. Following this the booklet covered possible side effects and included bleeding and listed other common side effects including bleeding in your eyes (including red eye), in your stomach (dark/black blood in the stools), your bowel, from your rectum, from your nose, from your gums or blood found in the urine (on testing); anaemia and what it might cause patients to feel and that blood tests might show an increase in gammaglutamyltransferase (GGT). It stated that further information on possible side effects can be found in the patient information leaflet.

Booklet two (432UK1900396-02; date of preparation April 2019), which was according to the Alliance re-certified in June 2021 under the job code 432-GB-2100450 was a 32 page booklet titled 'Switching from Warfarin to Eliquis (apixaban)'. The Panel noted that the booklet discussed why and how to switch to Eliquis and included sections on 'Things to be aware of when taking Eliquis' and side effects similar to Booklet one above.

Booklet three (432UK1900396-03; date of preparation April 2019) which was according to the Alliance re-certified in June 2021 under the job code 432-GB-2100451 was a 40 page booklet titled 'Helping to treat deep vein thrombosis and pulmonary embolism, and helping prevent recurrence'. This booklet started by explaining what venous thromboembolism, deep vein thrombosis and pulmonary embolism was, including what caused it and the signs and symptoms. The sections that followed discussed how VTE could be treated and the risk of recurrence of VTE be reduced. It then discussed Eliquis and included sections titled 'Things to note when taking Eliquis' and 'Possible side effects' which were similar to those described in Booklet one above.

The Panel noted that Booklet four which was available on the website at the time the complaint was made included the job code 432-GB-2100641 and date of preparation July 2021. The Panel noted that this 32-page booklet was titled 'Helping prevent blood clots after hip and knee replacement surgery' and covered what venous thromboembolism was and how it could be prevented including compression stockings, leg and foot exercises, drinking plenty of fluid and anticoagulants. It went on to discuss Eliquis and included a section on 'Things to be aware of when taking Eliquis' which was similar to that described in Booklet one above and a section titled 'Possible side effects' which stated 'Like all medicines, ELIQUIS® (apixaban) can cause side effects, although not everybody gets them. Like other similar medicines (anticoagulants), this medicine may cause bleeding which may potentially be life threatening. The bleeding may not be obvious and could possibly lead to anaemia (a low blood count which can cause tiredness or paleness). Other common side effects include bruising, blood in the urine (that stains the urine pink or red) and nausea (feeling sick). Further information on possible side effects can be found in the information leaflet inside your pack of tablets'.

The Panel noted the Alliance's submission that for all SPC and/or PIL updates, it undertook a robust review of active materials to determine whether any updates were required. According to the Alliance, changes to the SPC and PIL since April 2019 were not incorporated into the patient booklets because some of the changes were considered to be detailed topics (antiphospholipid syndrome, catheter ablation, and reversal agent) which were deemed to be particularly relevant to the prescriber and patients reading the booklets were referred to the PIL for these more detailed topics; only common and serious side effects were highlighted in the patient booklets and patients were referred to the PIL for a comprehensive list which would include rare, uncommon or unknown frequency adverse medicine reactions such as erythema multiforme

and hair loss; and some included language changes which did not alter the prescribing recommendations for apixaban.

SPC Revision 1 – May 2019

The Panel noted that according to the Alliance the changes to the SPC included the addition of a warning regarding thromboembolic risk in patients with antiphospholipid syndrome in May 2019 and the PIL was updated in this regard to include 'Take special care with Eliquis if you know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your doctor who will decide if the treatment may need to be changed'. The Panel noted that this change had not been included in the four booklets at issue.

The Panel noted that Section 4.4 Special Warnings and Precautions for use of the Eliquis SPC stated within a section titled 'Patients with antiphospholipid syndrome' that Direct acting Oral Anticoagulants (DOACs) including apixaban were not recommended for patients with a history of thrombosis who were diagnosed with antiphospholipid syndrome. In particular for patients that were triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

The Panel noted the Alliance's submission that the intention of the patient booklets was to provide patients who had already been prescribed apixaban with relevant and easily digestible information about their condition and treatment in a patient friendly format using appropriate language. According to the Alliance, the patient booklets were not intended to replace the comprehensive PIL, which was provided to all patients within their medication packaging and which the booklets referred readers to for further information. The patient booklets signposted patients to the PIL on numerous occasions to access the full information on apixaban.

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

Clause 6.1 stated, *inter alia*, that Information must be accurate, balanced, based on an up-to-date evaluation of all the evidence and reflect that evidence clearly and must not mislead.

The Panel noted that the 'Things to be aware of when taking Eliquis' section of the patient booklets stated 'You should not take Eliquis if you have (or are thought to have) a condition that increases the risk of serious bleeding, if you have liver disease leading to increased risk of bleeding or if you are taking medicines to prevent blood clotting. In addition, this medicine is not recommended in other instances such as pregnancy, breast feeding, in patients with prosthetic heart valves (with or without atrial fibrillation) and in patients taking certain other medications (please read the patient information leaflet for a full list). Please tell your doctor straight away if you think any of these apply to you. '

The Panel noted the purpose of the booklets in question as supplementary resources for patients who had already been prescribed apixaban and considered that failure to refer to the special warning with regards to antiphospholipid syndrome within the section 'Things to be aware of when taking Eliquis (apixaban)' particularly considering what was included within the section from the SPC was misleading. In the Panel's view, it was not sufficient to rely on the

patient information leaflet. Material had to be capable of standing alone with regard to the requirements of the Code and could not rely on qualification in either the patient information leaflet or a footnote. The Panel therefore ruled a **breach of Clause 6.1** in relation to each of the four booklets in this regard.

SPC Revision 2 – July 2019

2a. The Panel noted that according to the Alliance in July 2019, the Eliquis SPC was updated to include that patients undergoing catheter ablation (NVAF) could continue apixaban. The Panel noted that Section 4.2 Posology and method of administration and Section 4.4 Special warnings and precautions for use of the SPC stated that Patients can continue apixaban use while undergoing catheter ablation (see sections 4.3, 4.4 and 4.5). Section 4.3 Contraindications and Section 4.5 Interactions with other medicinal products and other forms of interaction of the Eliquis SPC were updated to state that concomitant treatment with any other anticoagulant agent was contraindicated, except under specific circumstances including when UFH [unfractionated heparin] was given during catheter ablation for atrial fibrillation. The PIL was updated to add except when, *inter alia*, a tube is inserted into your blood vessel (catheter ablation) to treat an irregular heartbeat (arrythmia) as an example of when you could take Eliquis whilst taking a medicine to prevent blood clotting. The Panel noted that this change had not been included in the four booklets at issue.

The Panel noted that the section on 'Things to be aware of when taking Eliquis (apixaban)' within the patient booklets stated that certain medicines and supplements can interfere with the anticoagulant effects of this medicine, increasing the risk of bleeding or making it less effective. A list of medicines that might affect ELIQUIS (apixaban) can be found in the patient information leaflet inside the medicine package'. It further stated you should not take Eliquis if, *inter alia*, you are taking medicines to prevent blood clotting.

The Panel considered that inclusion of 'you should not take Eliquis if you are taking medicines to prevent blood clotting' was inaccurate; there were specific circumstances when you could, including when UFH was given during catheter ablation for atrial fibrillation and it therefore ruled a **breach of Clause 6.1** in relation to each of the four booklets in this regard.

2b. Also in July 2019, according to the Alliance alopecia was added as an adverse event in Section 4.8 of the Eliquis SPC Undesirable effects as rare or uncommon depending on the indication and according to the Alliance, the PIL was updated to include hair loss as an uncommon side effect (may affect up to 1 in 100 people) in stroke prevention in non-valvular AF; treatment of DVT/PE and prevention of recurrence of DVT/PE and a rare side effect in VTE prevention after hip/knee operation. The Panel noted the Alliance's submission that only common and serious side effects were highlighted in the patient booklets; patients were referred to the PIL for a comprehensive list which would include rare, uncommon or unknown frequency adverse medicine reactions such as hair loss. The Panel noted that the list of side effects in each booklet was followed by the statement that 'Further information on possible side effects can be found in the patient information leaflet inside your tablet pack. Tell your doctor, nurse or pharmacist about any side effects you experience, even if they are not listed in the patient information leaflet or this booklet'.

The Panel did not consider that failure to include hair loss in the patient booklets meant that the booklets were inaccurate or not up-to-date as alleged and it ruled **no breach of Clause 6.1** in relation to each of the four booklets in this regard.

2c. Also in July 2019, according to the Alliance, the section in the SPC regarding Patients undergoing cardioversion was updated to include exclusion of left atrial thrombus using an image guided approach (eg transesophogeal echocardiography (TEE) or computed tomographic scan (CT)) prior to cardioversion should be considered, in accordance with established medical guidelines. The Panel did not consider that the exclusion of such information in the booklets aimed at patients was misleading and **no breach of Clause 6.1** was ruled in relation to each of the four booklets in this regard.

SPC Revision 3 – October 2019

3a. The Panel noted that according to the Alliance, in October 2019, the SPC was updated on the availability of the reversal agent andexanet alfa (Ondexxya) and the PIL was updated to state that 'If you take more Eliquis than recommended, you have an increased risk of bleeding. If bleeding occurs, surgery, blood transfusions, or other treatments that may reverse factor Xa activity may be required'. The Panel noted that the SPC provided by the Alliance did not appear to refer to andexanet alfa or Ondexxya.

Nonetheless, the Panel noted that each booklet contained information within the Frequently Asked Questions titled 'what should I do if I take too much', which stated 'tell your doctor immediately if you have taken more than the prescribed dose. Take the medicine pack with you, even if there are no tablets left. If you take more tablets than recommended, you may have an increased risk of bleeding'.

In this regard, the Panel did not consider that failure to include reference to reversal agents meant that the booklets were in breach of **Clause 6.1** as alleged, and **no breach** was ruled in relation to each of the four booklets in this regard.

3b. The Panel noted that according to the Alliance it appeared that the PIL but not the SPC was updated in October 2019 to state that Eliquis contains sodium and that this medicine contains less than 1mmol of sodium (23mg) per tablet, that is to say essentially 'sodium-free'. The Panel noted that the booklets in question did not mention sodium, but under 'Things to be Aware of When Taking Eliquis', stated that 'You should not take ELIQUIS® (apixaban) if you are allergic to any of the ingredients'.

The Panel noted that the complainant bore the burden of proof, and that he/she had not established that the update to the PIL was such that information in the patient booklets was not accurate or up to date in line with the Eliquis SPC in and therefore it ruled **no breach of Clause 6.1** in relation to each of the four booklets in this regard.

SPC Revision 4 and 5 – February and March 2020

The Panel noted that, according to the Alliance, further updates in February and March 2020 included the addition of fluconazole as a specific example of an inhibitor of CYP3A4 and P-gp, and an update to reflect the results of study CV185-316 (AUGUSTUS). No changes to the PIL occurred as a result except for the date of revision in February 2020.

The Panel noted that Section 4.5 of the Eliquis SPC Interaction with other medicinal products and other forms of interaction stated that the use of apixaban was not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp. It

went on to give examples of active substances which were not considered strong inhibitors of both CYP3A4 and P-gp, which included fluconazole, and stated that they were expected to increase apixaban plasma concentration to a lesser extent and that no dose adjustment for apixaban was required when co-administered with agents that were not strong inhibitors of both CYP3A4 and P-gp.

The Panel noted that the patient booklets, under the heading 'Things to be Aware of When Taking Eliquis' stated that 'certain medicines and supplements can interfere with the anticoagulant effects of this medicine, increasing the risk of bleeding or making it less effective. A list of medicines that might affect ELIQUIS® (apixaban) can be found in the patient information leaflet inside the medicine package'.

The Panel, noting the above, did not consider that failure to specifically refer to fluconazole or the study results within the patient booklets meant that the patient booklets were inaccurate or not up-to date as alleged and **no breach of Clause 6.1** was ruled in relation to each of the four booklets in this regard.

SPC Revision 6 – August 2020

The Panel noted that according to the Alliance in August 2020 angioedema was added as an adverse drug reaction in Section 4.8 of the Eliquis SPC, but there were no corresponding updates to the PIL apart from the date of revision.

The Panel noted that angioedema was listed in the SPC as an adverse reaction of unknown frequency (cannot be estimated from the available data) for NVAF [non-valvular atrial fibrillation] and VTEt [venous thromboembolism treatment] respectively.

The Panel noted the Alliance's submission that only common and serious side effects were highlighted in the patient booklets; patients were referred to the PIL for a comprehensive list which would include rare, uncommon or unknown frequency adverse medicine reactions. The Panel noted that the list of side effects in each booklet was followed by the statement that 'Further information on possible side effects can be found in the patient information leaflet inside your tablet pack. Tell your doctor, nurse or pharmacist about any side effects you experience, even if they are not listed in the patient information leaflet or this booklet'.

Whilst the Panel queried why there was no corresponding update to the PIL following the addition of angioedema to the SPC, the Panel did not consider that failure to include angioedema in the patient booklets meant that the booklets were inaccurate or not up-to-date as alleged and based on the complainant's allegation it ruled **no breach of Clause 6.1** in relation to each of the four booklets in this regard.

SPC Revision 7 – January 2021

The Panel noted that according to the Alliance, in January 2021, the SPC was changed from 'Apixaban is not recommended during pregnancy' to 'As a precautionary measure, it is preferable to avoid the use of apixaban during pregnancy' and only editorial changes were made to the PIL in this regard.

The Panel noted that the patient booklets stated that 'this medicine is not recommended in other instances such as pregnancy and to tell your doctor straight away if you think any of these apply to you'.

The Panel, noting the above, did not consider that the information in the booklets in relation to pregnancy was inaccurate or not up to date and **no breach of Clause 6.1** was ruled in relation to each of the four booklets in this regard.

SPC Revision 8 – March 2021

The Panel noted that according to the Alliance in March 2021, erythema multiforme was included as an adverse drug reaction in Section 4.8 of the Eliquis SPC and the PIL was updated to include 'Skin rash which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (erythema multiforme)' as a side effect of unknown frequency when used for VTE prevention after hip/knee operation and treatment of DVT/PE and prevention of recurrence of DVT/PE, and a very rare side effect when used for stroke prevention in non-valvular AF and at least one additional risk factor, which the Panel noted reflected the SPC.

The Panel noted the Alliance's submission that only common and serious side effects were highlighted in the patient booklets; patients were referred to the PIL for a comprehensive list which would include rare, uncommon or unknown frequency adverse medicine reactions such as Erythema multiforme. The Panel noted that the list of side effects in each booklet was followed by the statement that 'Further information on possible side effects can be found in the patient information leaflet inside your tablet pack. Tell your doctor, nurse or pharmacist about any side effects you experience, even if they are not listed in the patient information leaflet or this booklet'.

The Panel did not consider that failure to include Erythema multiforme in the patient booklets meant that the booklets were inaccurate or not up-to-date as alleged and it ruled **no breach of Clause 6.1** in relation to each of the four booklets in this regard.

SPC Revision 9 and 10 – April and May 2021

The Panel noted that according to the Alliance, in April and May 2021 various editorial changes were made to the NI and GB SPCs which had no impact on the PIL. The Panel did not consider that these changes would affect the content of the patient booklets and thus it ruled **no breach of Clause 6.1** in relation to each of the four booklets in this regard.

The Panel noted it's comments and rulings of breaches of Clause 6.1 above and considered that the Alliance had failed to maintain high standards and a **breach of Clause 5.1** was ruled in this regard.

Although the Panel was concerned with the omission of the warning regarding thromboembolic risk in patients with antiphospholipid syndrome and advice that readers should not take Eliquis if they are taking medicines to prevent blood clotting, when they could, in certain specific circumstances, it nonetheless noted that readers were signposted to the PIL prior to downloading the patient booklets and were referred to the PIL on a number of occasions throughout the four booklets where full information on apixaban could be accessed including the information above. Further, the Panel noted that the booklets reminded readers to inform health

professionals that they were taking Eliquis if having any surgical or dental procedures and about any other medicines that they were taking.

Noting the above, the Panel considered that its ruling of a breach for failing to maintain high standards adequately covered its concerns on this point. On balance, the Panel did not consider that the complainant had established that patient safety had been prejudiced as referred to in the supplementary information to Clause 2 of the Code as alleged. In the particular circumstances of this case, the Panel therefore, and on balance, ruled **no breach of Clause 2** which was used as a sign of particular censure and reserved for such use.

Complaint received **4 January 2022**

Case completed **9 March 2023**