CASE AUTH/3289/12/19 and AUTH/3290/12/19

COMPLAINANT v BRISTOL-MYERS SQUIBB AND PFIZER

Eliquis prescribing information

A complainant who described him/herself as a concerned UK health professional, complained that prescribing information attached to a promotional email for Eliquis (apixaban), sent by the Bristol-Myers Squibb/Pfizer Alliance and received in December 2019, did not include recent updates to the summary of product characteristics (SPC). Eliquis was indicated as an anticoagulant in certain patient groups.

The complainant noted that the prescribing information in question was last revised in July 2019 despite the SPC last being updated in October 2019. The changes made to the SPC related to the availability of an agent to reverse the anticoagulant activity of Eliquis (Section 4.4 of the SPC) and information on how to manage an overdose (Section 4.9 of the SPC). The July 2019 prescribing information was thus out of date and put patient safety at risk.

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

The Panel noted that the prescribing information in question contained a paragraph headed 'Haemorrhage risk' which stated 'Carefully observe for signs of bleeding. Use with caution in conditions with increased risk of haemorrhage. Discontinue administration if severe haemorrhage occurs'. This wording reflected the first paragraph of the sub-section headed 'Haemorrhagic risk' in Section 4.4 of the SPC. That first paragraph in the SPC was followed by another short paragraph and the statement, added in the October 2019 update, that an agent to reverse the anticoagulant activity of Eliquis was available. (In the October 2019 update, the availability of a reversal agent had also been added to Section 4.9 Overdose of the SPC). Having read the wording in the prescribing information, the Panel noted that it was not, however, until the reader had read a further four short paragraphs and they got to the end of the next short paragraph headed 'Surgery and invasive procedures' that they would read 'For information on reversal and managing bleeding, see SPC for further details'. There was no reference in the prescribing information to any antidote and nor was there any reference to overdose.

The Panel noted that the prescribing information did not have to include all of the detail from the SPC but what was provided must be sufficient to alert prescribers to some of the problems that might be encountered. Overall, the Panel considered that the information provided in the prescribing information about haemorrhagic risk was sufficient ie 'Carefully observe for signs of bleeding. Use with caution in conditions with increased risk of haemorrhage. Discontinue administration if severe haemorrhage occurs' and 'For information on reversal and managing bleeding, see SPC for further details' and so in that regard it ruled no breach of the Code. Given the clinical implications of haemorrhage, however, it was not helpful to the reader to have the information split – in the Panel's view, all of the relevant information should have been

under the heading of 'Haemorrhagic risk' even if the reference to the SPC was repeated elsewhere. Prescribing information was an important component of patient safety and companies should ensure that it was provided in such a way that prescribers found the information they needed quickly and easily. Where clinical events could be serious, physicians should be immediately alerted that more information was available in the SPC. The Panel accepted that the prescribing information was headed 'Consult summary of product characteristics prior to prescribing' but it nonetheless considered that, on balance, high standards had not been maintained. A breach of the Code was ruled.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and reserved for such. The Panel did not consider that the circumstances of this case warranted a ruling of a breach of Clause 2 and no breach was ruled.

A complainant who described him/herself as a concerned UK health professional, complained that prescribing information attached to a promotional email for Eliquis (apixaban), sent by the Bristol-Myers Squibb/Pfizer Alliance and received on 16 December 2019, did not include recent updates to the summary of product characteristics (SPC). Eliquis was indicated as an anticoagulant in certain patient groups.

COMPLAINT

The complainant noted that the prescribing information attached to the email sent in December 2019 was last revised in July 2019 despite the SPC last being updated in October 2019. The changes made to the SPC related to the availability of an agent to reverse the anticoagulant activity of Eliquis (Section 4.4 of the SPC) and information on how to manage an overdose (Section 4.9 of the SPC). The complainant was concerned that the July 2019 prescribing information was thus out of date and put patient safety at risk.

When writing to Bristol-Myers Squibb and Pfizer, the Authority asked them to consider the requirements of Clauses 2, 4.1 and 9 of the Code.

RESPONSE

Bristol-Myers Squibb and Pfizer (the Alliance) submitted a joint response and explained that Bristol-Myers Squibb, on behalf of the Alliance, maintained all regulatory updates relating to Eliquis including the product's prescribing information.

Bristol-Myers Squibb stated that it had a defined and robust process in place to review all regulatory updates and amendments to the Eliquis SPC. A multidisciplinary team across the Alliance systematically reviewed and assessed all upcoming SPC updates and provided the appropriate recommendations to update the Eliquis prescribing information. Any changes needed were then implemented into the Eliquis prescribing information to form a new version, replacing the previous prescribing information on all promotional material.

In 2019, the Eliquis SPC was updated twice. The first update on 1 July related to the use of the medicine in patients undergoing cardiac catheter ablation. The multidisciplinary team reviewed the SPC update and recommended that the Eliquis prescribing information be amended accordingly to provide that information. In addition, considering the advances in the management of bleeding in clinical practice and changes in the landscape at that time, the team

also requested that the warnings and precautions section should be updated to include the following, 'for information on reversal and managing bleeding, see SPC for further details'. This would direct health professionals to a comprehensive source document and ensure clarity on the specific strategies appropriate for management of bleeding related to the use of Eliquis. A copy of the July 2019 prescribing information was provided.

The second update to the SPC was in October 2019, as a consequence of a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) on 3 October 2019, for the approval to update the Eliquis SPC on the availability of a reversal agent. As a result, Sections 4.4 and 4.9 were updated to include the wording regarding the availability of a reversal agent and its use in the management of bleeding. The Alliance reviewed the updated SPC and the prescribing information in its entirety and concluded that no further changes were required to the latest Eliquis prescribing information because it already stated 'for information on reversal and managing bleeding, see SPC for further details'. Given that a number of strategies for the management of bleeding were described in the SPC, the Alliance considered it important to direct health professionals to the primary comprehensive source, the SPC, rather than try to precis it in the prescribing information; this was already clearly reflected in the latest prescribing information.

During the SPC update in October, the Alliance reviewed the content of all promotional and non-promotional material in circulation, which discussed management of bleeding, and amended those as necessary to reflect the availability of a reversal agent within the range of strategies described in the SPC.

The Alliance recognised the importance of Clause 4.1, which stated that prescribing information must be provided in a clear and legible manner in promotional material for a medicine and that the prescribing information must be consistent with the product SPC. The Alliance followed robust internal procedures during both SPC updates in 2019, and upon thorough review, concluded that the prescribing information did not warrant further changes in October as the wording already stated 'for information on reversal and managing bleeding, see SPC for further details.'.

The Alliance noted that the email in question included a prominent link to the current prescribing information, which was consistent with the SPC. The Alliance denied a breach of Clause 4.1.

The Alliance submitted that it had neither breached Clause 4.1 nor failed to maintain patient safety through the provision of the approved prescribing information. The Alliance operated to high standards, following robust internal instructions, working with a focus on patient safety, enhanced patient care and transparency, whilst appreciating the special nature of medicines. When SPC updates occurred, the multidisciplinary team reviewed the entire prescribing information and exercised a high degree of rigour, before it decided on whether revising the prescribing information was warranted. Following a uniform and stringent process enabled the Alliance to ensure that the Eliquis prescribing information was always up-to-date, complied with the Code and remained consistent with the SPC. In this instance, through referring health professionals in the prescribing information to the full and comprehensive information in the SPC in relation to reversal and management of bleeding, the Alliance submitted that it had maintained patient safety and maintained high standards. As a result, the Alliance denied a breach of Clause 9.1.

The Alliance also denied any breach of Clause 2; patient safety was paramount and the Alliance operated professionally and ethically to ensure the appropriate and safe use of its medicines including ensuring health professionals based clinical decisions on the full information available. The Alliance stated that it had not undermined confidence in the industry.

PANEL RULING

The Panel noted that the prescribing information in question contained a paragraph headed 'Haemorrhage risk' which stated 'Carefully observe for signs of bleeding. Use with caution in conditions with increased risk of haemorrhage. Discontinue administration if severe haemorrhage occurs'. This wording reflected the first paragraph of the sub-section headed 'Haemorrhagic risk' in Section 4.4 of the SPC. That first paragraph in the SPC was followed by another short paragraph and the statement, added in the October 2019 update, that that an agent to reverse the anticoagulant activity of Eliquis was available. (In the October 2019 update, the availability of a reversal agent had also been added to Section 4.9 Overdose of the SPC). Having read the wording in the prescribing information, the Panel noted that it was not, however, until the reader had read a further four short paragraphs and they got to the end of the next short paragraph headed 'Surgery and invasive procedures' that they would read 'For information on reversal and managing bleeding, see SPC for further details'. There was no reference in the prescribing information to any antidote and nor was there any reference to overdose.

The Panel noted that the Code required prescribing information to include, amongst other things, a succinct statement of serious adverse reactions and precautions. The prescribing information thus did not have to include all of the detail from the SPC but what was provided must be sufficient to alert prescribers to some of the problems that might be encountered. Haemorrhagic risk, whether through overdose or otherwise, was clearly a possibility with an anticoagulant. Overall, the Panel considered that the information provided in the prescribing information about haemorrhagic risk was sufficient ie 'Carefully observe for signs of bleeding. Use with caution in conditions with increased risk of haemorrhage. Discontinue administration if severe haemorrhage occurs' and 'For information on reversal and managing bleeding, see SPC for further details' and so in that regard it ruled no breach of Clause 4.1. Given the clinical implications of haemorrhage, however, it was not helpful to the reader to have the information split – in the Panel's view, all of the relevant information should have been under the heading of 'Haemorrhagic risk' even if the reference to the SPC was repeated elsewhere. Prescribing information was an important component of patient safety and companies should ensure that it was provided in such a way that prescribers found the information they needed quickly and easily. In particular circumstances where clinical events could be serious, physicians should be immediately alerted that more information was available in the SPC. The Panel accepted that the prescribing information was headed 'Consult summary of product characteristics prior to prescribing' but it nonetheless considered that, on balance, high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and reserved for such. The Panel did not consider that the circumstances of this case warranted a ruling of a breach of Clause 2 and no breach was ruled.

Complaint received **17 December 2019**

Case completed **21 and 25 August 2020**