CASE AUTH/3889/4/24 ***NO BREACH OF THE CODE***

COMPLAINANT/CHIEF EXECUTIVE v BAYER

Allegations about a promotional email and a breach of undertaking

CASE SUMMARY

This case was in relation to an email sent by a third party on Bayer's behalf that was promotional for Xarelto (rivaroxaban). The complainant, referring to renal impairment, alleged that the email included no mention of any contraindications or special warnings.

The outcome under the 2021 Code was:

No Breach of Clause 2	**Requirement that activities or materials must not bring discredit upon, or reduce confidence in, the pharmaceutical industry**
No Breach of Clause 3.3	**Requirement to comply with an undertaking given in relation to a ruling under the Code**
No Breach of Clause 5.1	**Requirement to maintain high standards at all times**
No Breach of Clause 6.1	**Requirement that material must be sufficiently complete to enable recipients to form their own opinion of the therapeutic value of the medicine**

This summary is not intended to be read in isolation.
For full details, please see the full case report below.

FULL CASE REPORT

A complaint about Bayer was received from an anonymous, contactable complainant. The complaint concerned an alleged breach of undertaking. As the PMCPA was responsible for ensuring compliance with undertakings, the complaint was also taken up in the name of the Director (now known as the Chief Executive).

COMPLAINT

The complaint wording is reproduced below:

> "Please see the following promotional advert from Bayer.
>
> No mention is made of any contraindications or special warnings. Especially of note, is the following in section 4.4:

Renal impairment

In adult patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2).

Xarelto should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations (see section 4.5).

Xarelto is not recommended in children and adolescents with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m2), as no clinical data is available

Given the patients that are likely to be placed upon this treatment (the elderly), renal impairment is a likely co-morbidity; there is a more theoretical issue that there could be children or adolescents who also should not be on treatment.

Please review case AUTH/3035/4/18 where exactly this same point is made and then this omission was viewed as a patient safety matter. It seems nothing seems to have been learned."

When writing to Bayer, the PMCPA asked it to consider the requirements of Clauses 3.3, 6.1, 5.1 and 2 of the 2021 Code.

BAYER'S RESPONSE

The response from Bayer is reproduced below:

"The complaint is in relation to a promotional email and an alleged breach of undertaking, therefore in breach of the 2021 ABPI Code of Practice clauses 3.3, 6.1, 5.1 and 2.

Bayer plc. ("Bayer") have investigated the matter and disagree with the alleged breach of the undertaking given in Case AUTH/3035/4/18 (clause 3.3), as well as the alleged breach of clauses 6.1, 5.1 and 2 of the 2021 ABPI Code of Practice. Our response and rationale for our rejection are detailed below:

The Bayer promotional email has been certified by a Bayer final signatory appropriately qualified and registered with the MHRA and PMCPA: [details provided] and subsequently sent on the [date] February 2024 via the third-party organisation, [named], to verified general practitioners from the UK.

The subject line of this email is "Help protect your patients with NVAF and diabetes from a stroke – Bayer PLC". This email shows the picture of an elderly man, a fictional patient who is 78 years old and has non-valvular atrial fibrillation (NVAF) and diabetes, with a disclaimer next to the image that highlights that this case is a fictional case and the picture used is of a model. As the disclaimer asserts that the case in this email is

fictional, it is unreasonable to infer other likely co-morbidities not detailed in this email to this fictional case. Whilst real-life elderly people with NVAF may have multiple comorbidities, this email's focus was clearly on those with NVAF and the isolated co-morbid risk factor, diabetes. The email then states that the relative stroke risk of patient with NVAF and diabetes is 70% higher than those without diabetes. Patients with diabetes are at increased risk of cardiovascular death than the general population.

Additionally, the email invites the reader to "see how Xarelto® (rivaroxaban) could help prevent stroke and systemic embolism in patients with NVAF and diabetes" by accessing a webpage on a Bayer promotional product website. The webpage focuses on patients with NVAF and diabetes and includes a link to rivaroxaban prescribing information as well as the following disclaimers:

"Rivaroxaban should be used with caution in patients with CrCl 15-29 ml/min and in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations. Use is not recommended in patients with CrCl < 15 ml/min."

"Use of rivaroxaban is not recommended in those with end stage renal impairment (creatinine clearance < 15mL/min). Rivaroxaban can be used in those with a creatinine clearance 15-29 mL/min, provided it is done with caution. Rivaroxaban should also be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentration."

The purpose of the email was to encourage the readers to access and consider educational product information and materials hosted on the promotional website. They would then make their own opinion on the suitability of rivaroxaban for their patients with NVAF and diabetes in routine practice. The content of the email and the Bayer promotional product website in no way give undue reassurance or confidence on the use of rivaroxaban without any consideration for its precautions for use, special warnings, and the like. Prior to the reader being directed to the Bayer promotional product website, the wording above the "FIND OUT MORE" link states:
"See how Xarelto® (rivaroxaban) <u>could</u> help prevent stroke and systemic embolism in patients with NVAF and diabetes."

In Case AUTH/3035/4/18, an anonymous complainant who described him/herself as a concerned UK health professional complained about a Xarelto advertisement by Bayer. The advertisement at issue was headed "Xarelto Protects Your High-Risk NVAF [non-valvular atrial fibrillation] Patients with Confidence"; the second of three bullet points below read "In your patients with renal impairment". The Panel considered that this advertisement implied that rivaroxaban could be used with confidence in patients with renal impairment, regardless of people's creatinine clearance. A breach of clauses 2, 7.2, 7.4 and 9.1 [2016 ABPI Code] were then ruled.

Bayer disagrees with the alleged breach of undertaking referring to AUTH/3035/4/18. Unlike [the] Bayer advertisement, the promotional email does not imply that Xarelto can be used with confidence in patients with renal impairment. It specifically refers to a fictional patient with a focus on NVAF and diabetes. Therefore, no other specific comorbidities were mentioned, nor should any other comorbidities be assumed for this

fictional patient. The email does not mention nor imply that rivaroxaban can be used in patients with NVAF and renal impairment.

The email includes a link to a Bayer website which promotes rivaroxaban to UK healthcare professionals. The webpage, whilst dedicated to the management of patients with NVAF and diabetes, includes statements from Xarelto's Summary of Product Characteristics in relation to its prescription in patients with NVAF and renal impairment, including statements from sections 4.2 (Posology and method of administration) and 4.4 (Special warnings and precautions for use), and a link to Xarelto's prescribing information.

The promotional email shows the picture of a fictional patient with NVAF and diabetes, that is an elderly patient. Xarelto is indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. Atrial fibrillation (AF) is more common in older people, and it is estimated that about 10% of people over 65 may have atrial fibrillation. According to recent literature on the epidemiology of AF worldwide, more than 70% of AF patients in Western Europe, Australia and North America were aged >65 years. Also, recent UK population study reports the mean age at AF diagnosis between 1998-2017 was 78.0 years. Similarly for the mean age of onset of type 2 diabetes, in a UK retrospective cohort study (between 2009-2018), the mean age of diagnosis for type 2 diabetes in the UK was 60.4 in men and 61.7 in women. [References provided] Hence, the theoretical issue that the email in question, referring to patients with NVAF and diabetes, could be misinterpreted by a UK general practitioner as being relevant to a paediatric population is unreasonable. Children and adolescent are less likely to be diagnosed with NVAF, therefore the email did not require and does not include a statement indicating that the safety profile and efficacy of Xarelto in children 0 to <18 years have not been established in this indication.

In conclusion Bayer disagrees with the alleged breaches of clauses 3.3, 6.1, 5.1 and 2 of the 2021 ABPI Code of Practice as outlined in our response."

PANEL RULING

This complaint related to an email sent by a third party on Bayer's behalf that was promotional for Xarelto (rivaroxaban) and had the subject line "Help protect your patients with NVAF and diabetes from a stroke – Bayer PLC". The complainant alleged that the email included no mention of any contraindications or special warnings and cited an extract of Section 4.4 of the Xarelto summary of product characteristics which related to renal impairment. The complainant also made reference to Case AUTH/3035/4/18 and Bayer was asked to respond in relation to a potential breach of undertaking.

The Panel noted that Xarelto was an antithrombotic agent indicated for the treatment of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

The Panel noted that, as cited by the complainant in relation to renal impairment, Section 4.4 of the Xarelto 20 mg summary of product characteristics stated:

> "In patients with severe renal impairment (creatinine clearance <30 ml/min) rivaroxaban plasma levels might be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk. Xarelto is to be used with caution in patients with creatinine clearance 15–29 ml/min. Use is not recommended in patients with creatinine clearance <15 ml/min.
> Xarelto should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations.
> Xarelto is not recommended in children and adolescents with moderate or severe renal impairment (glomerular filtration rate <50 ml/min/1.73 m^2), as no clinical data is available."

The Panel noted the complainant's statement that renal impairment was a likely comorbidity for patients likely to be prescribed Xarelto ("the elderly"), while the warnings and precautions for children and adolescents were a more theoretical issue.

The Panel acknowledged that Clause 6.1 of the Code did not require expressly for special warnings and precautions for use to be included in materials. However, Clause 6.1 did require, among other things, that material must be sufficiently complete to enable recipients to form their own opinion of the therapeutic value of the medicine.

The Panel considered that whether a warning or precaution needed to be highlighted within the main body of promotional material, in addition to the requirement for it to be included within the prescribing information, depended on a consideration of all the circumstances. This would include taking account of the therapy area and the nature of the warning, as well as the content, layout, audience and intended use of the material.

The Panel noted the complainant had stated 'No mention is made of any contraindications or special warnings' but had only referred to renal impairment. As no other special warnings and precautions for use or contraindications had been identified by the complainant the Panel limited its consideration to renal impairment.

The Panel took account of the content of the email, which appeared to be focused on the risk of stroke in patients with non-valvular atrial fibrillation (NVAF) and diabetes. There was a large call to action in the middle of the email to "See how Xarelto (rivaroxaban) could help prevent stroke and systemic embolism in patients with NVAF and diabetes." A second, smaller, call to action appeared towards the end of the email after a short section on shared decision-making and choosing an anticoagulant: "Help protect patients, like Joe, with NVAF and diabetes from a stroke". There was no mention within the email of any other potential comorbidities, such as renal impairment. The 78-year-old patient in the fictitious case study (Joe) was only described as having NVAF and diabetes. The email made no mention of prescribing Xarelto in patients with renal impairment.

The Panel noted Bayer's submission that the email linked through to a webpage which included disclaimers about the use of rivaroxaban in patients with renal impairment. The email itself included a link to prescribing information. The Panel was not provided with a copy of the prescribing information and therefore had no information before it about what information relating to special warnings and precautions for use and contraindications was included.

The Panel noted Bayer's submission that the email was sent to verified general practitioners from the UK. The Panel considered that, on the balance of probabilities, the target audience of general practitioners would be likely to exercise caution before prescribing any medicine to

patients with renal impairment and that similar caution was likely before prescribing antithrombotic medication and particularly so in elderly patients. In the Panel's view general practitioners would therefore be unlikely to rely on the email alone, without further research, to make a prescribing decision.

The Panel noted the contraindications and special warnings in the summary of product characteristics but as no others had been specifically raised by the complainant, the Panel did not consider their relevance to the advertisement at issue.

Having carefully considered the material before it the Panel concluded that the content of the email did not misleadingly imply that there were no warnings or precautions to be considered in relation to the use of Xarelto in patients with renal impairment.

The Panel therefore ruled **no breach of Clause 6.1** in relation to the complainant's allegation that the email did not include contraindications or special warnings.

The complainant had cited Case AUTH/3035/4/18, which concerned a Xarelto advertisement. The advertisement at issue in that case had the headline "Xarelto Protects Your High-Risk NVAF Patients with Confidence" and the second of three bullet points below read "In your patients with renal impairment". The Panel in that case ruled a breach of the Code because it considered that the claim implied that Xarelto could be used with confidence in all NVAF patients with renal impairment, which was not so. However in the email at issue in this case (Case AUTH/3889/4/24) there was no mention of prescribing Xarelto in patients with renal impairment.

The Panel considered that the current case was not closely similar to Case AUTH/3035/4/18. In particular, the Panel noted the differences between the content of the promotional material at issue and its ruling of no breach of Clause 6.1, above. For these above reasons, the Panel did not consider that Bayer had breached the undertaking given in Case AUTH/3035/4/18 and therefore ruled **no breach of Clause 3.3**.

The Panel noted the complainant's comment about omission of the renal impairment information having been viewed as a matter of patient safety in Case AUTH/3035/4/18. The Panel also considered that an undertaking was an important document. However, given its rulings of no breaches of Clauses 3.3 and 6.1, above, the Panel considered that there was not evidence that Bayer had failed to maintain high standards. The Panel ruled **no breach of Clause 5.1**.

The Panel noted that the supplementary information to Clause 2 included inadequate action leading to a breach of undertaking and prejudicing patient safety as examples of activities likely to be in breach of Clause 2. Having ruled no breach of Clauses 3.3, 6.1 and 5.1 above, the Panel ruled **no breach of Clause 2**.

Complaint received **16 April 2024**

Case completed **8 April 2025**