CASE AUTH/3705/11/22 ***NO BREACH OF THE CODE***

COMPLAINANT v ABBVIE

Allegations about the dosing information for Rinvoq on AbbVie's website

CASE SUMMARY

This case was in relation to dosing information about Rinvoq on AbbVie's product website.

The Panel ruled no breach of the following Clauses of the 2021 Code, as the Panel did not consider that within the context of the discrete section of the webpage, that the claim at issue misleadingly implied that Rinvoq could be taken with any type of food, including grapefruit, as alleged. The Panel considered that the claim in question was capable of substantiation, and did not consider that the complainant had demonstrated that AbbVie had failed to maintain high standards, or consequently brought discredit upon, or reduced confidence in, the pharmaceutical industry.

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 5.1	**Requirement to maintain high standards**
No Breach of Clause 6.1	**Requirement that information, claims and comparisons must not be misleading**
No Breach of Clause 6.2	**Requirement that information, claims and comparisons must be capable of substantiation**

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 was received from an anonymous, contactable complainant about dosing information for Rinvoq (upadacitinib) on AbbVie's product website.

COMPLAINT

The complainant stated that the dosing information for Rinvoq, which was indicated for arthritis, was incorrect and not consistent with the summary of product characteristics (SPC). The complainant provided a link to the dosing webpage. In the section titled, 'dosing recommendations', the following was written: 'The recommended dose of RINVOQ is one 15-mg tablet once a day, with or without food'. The complainant noted, however, that the SPC recommended that any food containing grapefruit should be avoided (Section 4.2). The complainant alleged that this important information was completely omitted from the webpage and the claim around dosing. As the claim on the page stated 'with food', this would imply it was fine to take the medicine with any kind of food. However, food mixed with grapefruit would lead to increased exposure to Rinvoq (Section 4.5 of

SPC) and an increase in side-effects. The complainant stated that this should have been made clear in this claim. It was even more important as Rinvoq was a black triangle medicine. It was concerning that a reviewer had approved this claim without mention of grapefruit. The complainant alleged that Clauses 5.1, 6.1, 6.2 and 2 had been breached.

When writing to AbbVie, the Authority asked it to consider the requirements of Clauses 2, 5.1, 6.1 and 6.2 of the Code as cited by the complainant.

RESPONSE

AbbVie stated that it took its responsibility for compliance with all applicable laws and regulations, including the Code, very seriously and the company continuously endeavoured to maintain these high standards in all of its activities.

AbbVie stated that the complainant alleged that the dosing information for Rinvoq, indicated for rheumatoid arthritis, as included on the AbbViePro website, was incorrect and not consistent with the SPC information. Specifically, the complainant alleged that the Rinvoq SPC recommended that any food containing grapefruit should be avoided and this information was completely omitted from the webpage and the claim around dosing. The complainant alleged breaches of Clauses 2, 5.1, 6.1 and 6.2 of the 2021 Code.

AbbVie stated that it took patient safety extremely seriously and wanted to reassure the Panel that all the appropriate and relevant information had been included for health professionals to understand the appropriate dosing of Rinvoq for their patients.

AbbVie submitted that the complaint was not substantiated and that, on the balance of probabilities, no breach of the Code had occurred in relation to the information regarding Rinvoq, as presented on the AbbViePro website. There were a number of areas on the Rinvoq section of the AbbViePro webpage where health professionals were informed that food or drink containing grapefruit should be avoided during treatment. Relevant screenshots were provided of the webpage's top navigation menu and links to both the Rinvoq Prescribing Guide (UK-UPAD-220185) and Rinvoq Prescribing Information (UK-UPAD-220221) with certain parts highlighted.

Once a health professional scrolled down the webpage relating to dosing, and prior to reaching the claim referenced by the complainant, the Prescribing Guide for health professionals could be found. This click-through document provided health professionals with all the relevant information for consideration prior to initiating Rinvoq for their patients, outlining information on dosing, screening, monitoring and safety recommendations. As noted above, this guide specifically called out that grapefruit-containing food or drink should be avoided, along with other relevant information.

> **'Starting patients on RINVOQ'**
>
> A convenient guide providing information on dosing, screening, monitoring and safety recommendations.'

A screenshot of the midsection of the dosing webpage was provided.

In addition, under the dosing recommendations there was text that recommended the health professionals to consult the SPC for further details regarding monitoring requirements and contraindications prior to initiating Rinvoq. Within this text, a link to the full product information

outlined in the Rinvoq Summary of Product Characteristics hosted on the EMC website could be obtained.

Finally, there was another link to the Rinvoq Prescribing Information at the bottom of the webpage and a relevant screenshot was provided.

The summary bullet points in the 'dosing recommendations' section of the website, that was flagged by the complainant, in fact directly reflected text included in Section 4.2 of the SPC under the heading 'Method of Administration' which stated:

> *'RINVOQ is to be taken orally once daily with or without food and may be taken at any time of the day. Tablets should be swallowed whole and should not be split, crushed, or chewed in order to ensure the entire dose is delivered correctly.'*

A screenshot of the summary bullet points was provided. The purpose of these bullet points was to summarise details for how Rinvoq could be taken, that it could be taken once a day, with or without food and that dosing was not constrained by timing requirements around mealtimes, as might be the case with many other medicines.

AbbVie stated that it would also like to point out that Section 4.2 in the SPC stated that treatment with upadacitinib should be initiated and supervised by physicians experienced in the diagnosis and treatment of conditions for which upadacitinib was indicated. The details relating to Rinvoq on the AbbViePro website were addressed at health professionals who met the level of expertise that would allow them to prescribe Rinvoq in the first place, and AbbVie considered that this had several important implications:

- There were numerous other considerations that a health professional needed to take into account when starting a patient on Rinvoq including, for example, blood counts and lab measures, vaccination information, information related to infections, etc., and this was all described in the SPC, the prescribing information and the Prescribing Guide for starting patients on Rinvoq, alongside the point related to food and drink containing grapefruit;

- on the balance of probabilities, and given the context of the website and the link to the medicine's method of administration, experienced health professionals that could prescribe Rinvoq were not likely to interpret the statement 'with or without food' as implying that Rinvoq could be taken with any and all types of food, including grapefruit, but rather that it meant Rinvoq did not need to be administered either with food, or on an empty stomach, as was the case with numerous medications;

- AbbVie recognised that health professionals were often busy and subject to time pressure. However, the company did not believe it would be reasonable to make an assumption that an experienced health professional looking to prescribe an advanced therapy would simply ignore signposted key sections of a website and instead make a prescribing decision based solely on one sentence in isolation. The complainant had not provided any evidence that, on the balance of probabilities, this was likely to be the case;

- it had been estimated that CYP3A4 metabolized about half of all drugs on the market, including paracetamol, ciclosporin and corticosteroids, all of which were commonly co-administered by physicians experienced in the diagnosis and treatment of conditions for which Rinvoq was indicated. Therefore, such physicians commonly considered the effect

that eating or drinking grapefruit juice might have on exposure levels to these medications and were experienced to make these considerations.

Lastly, regarding the complainant's statement that food mixed with grapefruit would lead to an increase in side-effects. The SPC stated that food or drink containing grapefruit should be avoided due to the known interaction of grapefruit and the CYP3A4 enzyme, so it was recommended that grapefruit be avoided. There were no specific data to show that there was an increase in side-effects with consumption of grapefruit- containing products.

Conclusion

AbbVie stated that it took its responsibility for compliance with the Code very seriously as it continuously endeavoured to maintain high standards in all its activities.

AbbVie stated that it believed that in this case high standards had been maintained at all times in the presentation of the dosing webpage, and such a webpage included multiple sources of information regarding precautions around food and drink containing grapefruit.

The information presented on the webpage was sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine and was not misleading. In addition, the information was accurate, balanced, fair, objective and unambiguous, and claims contained therein were capable of substantiation (referenced to the Rinvoq SPC).

The information and claims contained on the webpage did not prejudice patient safety and were consistent with the higher burden of responsibility resulting from the black triangle mark. The health professionals were explicitly advised to consult the Rinvoq SPC prior to initiating patients on treatment with Rinvoq and both the Prescribing Guide and the prescribing information were signposted several times on the page.

AbbVie stated that it remained available to answer any further questions but trusted that its response was sufficient for the Panel to confirm AbbVie was not in breach of any of the Clauses of the Code that AbbVie had been asked to consider.

PANEL RULING

The Panel noted that the complaint concerned the dosing information for Rinvoq on a webpage directed at health professionals. The Panel noted that the claim in question, within the section titled, 'Dosing recommendations', read 'The recommended dose of RINVOQ is one 15mg tablet once a day, with or without food'. The complainant noted, however, that Section 4.2 of the Rinvoq SPC recommended that any food containing grapefruit should be avoided. The complainant alleged that the phrase in question 'with food' implied that it was fine to take the medicine with any kind of food which was not the case as food mixed with grapefruit would lead to increased exposure to Rinvoq and an increase in side-effects.

The Panel noted the webpage at issue was a product webpage for UK health professionals only. At the top of the page was the Rinvoq (upadacitinib) 15mg tablets logo which included the black triangle adjacent to which were links to the Rinvoq prescribing guide, Rinvoq prescribing information and the adalimumab prescribing information. Below was a section titled 'Dosing' which stated 'RINVOQ is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-

modifying drugs (DMARDs). RINVOQ may be used as monotherapy or in combination with methotrexate[1]'.

Below a further menu bar, which indicated that the dosing webpage had been selected, was a pack shot alongside the claim 'Once-daily oral treatment for your adult patients with moderate to severe rheumatoid arthritis[1]', 'One dose, one tablet, once a day' which sat above a section titled 'Starting patients on RINVOQ' which contained a link to the prescribing guide described as a 'A convenient guide providing information on dosing, screening, monitoring and safety recommendations'.

The following section was titled 'Dosing recommendations' and contained three horizontal images with text beneath each; the first was an image of a Rinvoq tablet above the claim in question, 'The recommended dose of RINVOQ is one 15-mg tablet once a day, with or without food'; the second image was of a broken Rinvoq tablet surrounded by a circle with a diagonal line through it above the statement 'Tablets should be swallowed whole, and should not be split, crushed, or chewed'. The third image was of a clockface with the statement 'RINVOQ may be taken at any time of the day; patients may find it easier to take RINVOQ at the same time every day to help them remember to take it' beneath. At the bottom of the page in much smaller font size was the statement 'Please consult the Summary of Product Characteristics [as a hyperlink] for further details regarding monitoring requirements and contraindications prior to initiating RINVOQ'.

The Panel noted AbbVie's submission that there were a number of areas on the Rinvoq section of the AbbViePro webpage where health professionals were informed that food or drink containing grapefruit should be avoided during treatment and, in this regard, referred to both the Rinvoq prescribing guide and the Rinvoq prescribing information. The Panel also noted AbbVie's submission that there was a reference to consulting the Summary of Product Characteristics at the bottom of the webpage, albeit in much smaller font than the rest of the page. The Panel, however, considered that each claim had to be capable of standing alone in relation to the requirements of the Code and could not be qualified by information in linked material to ensure Code compliance.

The Panel noted that that Section 4.2 of the Rinvoq SPC, Posology and method of administration, Method of administration stated 'RINVOQ is to be taken orally once daily with or without food and may be taken at any time of the day. Tablets should be swallowed whole and should not be split, crushed, or chewed in order to ensure the entire dose is delivered correctly'. A separate paragraph stated that 'Food or drink containing grapefruit should be avoided during treatment with upadacitinib (see section 4.5)'. Section 4.5 of the Rinvoq SPC, Interactions with other medicinal products and other forms of interaction, Co-administration with CYP3A4 inhibitors, stated, amongst other things, that 'upadacitinib exposure is increased when co-administered with strong CYP3A4 inhibitors' and listed 6 such inhibitors including grapefruit juice. The final paragraph of Section 4.5 Co-administration with CYP3A4 inhibitors stated that 'Coadministration of upadacitinib with grapefruit may increase exposure to upadacitinib. Food or drink containing grapefruit should be avoided during treatment with upadacitinib'. The Panel noted that the reference to grapefruit consumption did not appear in either Section 4.3 Contraindications or Section 4.4 Special warnings and precautions for use.

The Panel noted AbbVie's submission that the purpose of the relevant section of the webpage was to summarise details for how Rinvoq could be taken, that it could be taken once a day, with or without food and that dosing was not constrained by timing requirements around mealtimes, as might be the case with many other medicines. AbbVie stated that the claim in question directly reflected text included in Section 4.2 of the SPC under the heading 'Method of Administration'. AbbVie further stated that experienced health professionals that could prescribe Rinvoq were not

likely to interpret the statement 'with or without food' as implying that Rinvoq could be taken with any and all types of food, including grapefruit, but rather that it meant Rinvoq did not need to be administered either with food, or on an empty stomach, as was the case with numerous medications. The Panel also noted AbbVie's submission that it had been estimated that CYP3A4 metabolized about half of all medicines on the market, including paracetamol, ciclosporin and corticosteroids, all of which were commonly co-administered by physicians experienced in the diagnosis and treatment of conditions for which Rinvoq was indicated and therefore, such physicians commonly considered the effect that eating or drinking grapefruit juice might have on exposure levels to these medications and were experienced to make these considerations.

The Panel considered that whether the SPC statement that 'food or drink containing grapefruit should be avoided during treatment with Rinvoq' should be referred to when discussing the administration of Rinvoq should be decided on a case-by-case basis; relevant factors would include the content and nature of the material. In the particular circumstances of this case, the Panel considered that the section of the webpage in question briefly summarised, with accompanying images, the practical aspects of administration including that the tablet should be swallowed whole, should not be split, crushed, or chewed, could be taken at any time of day and the claim in question, 'The recommended dose of RINVOQ is one 15-mg tablet once a day, with or without food'. Within the narrow context of this section, the Panel considered, on balance, that health professionals would consider that the statement in question was referring to whether or not the tablet could be taken on an empty stomach rather than making a broader and unqualified claim that Rinvoq could be consumed with any type of food including grapefruit, as alleged by the complainant. The Panel also bore in mind that Section 4.2 of the SPC stated 'Treatment with upadacitinib should be initiated and supervised by physicians experienced in the diagnosis and treatment of conditions for which upadacitinib is indicated'.

Noting its comments above, the Panel did not consider that within the context of the discrete section of the webpage that the claim 'The recommended dose of RINVOQ is one 15-mg tablet once a day, with or without food' misleadingly implied that Rinvoq could be taken with any type of food, including grapefruit, as alleged, and ruled **no breach of Clause 6.1** of the Code. The Panel further considered, noting its comments and ruling above, that the claim in question was capable of substantiation and ruled **no breach of Clause 6.2** of the Code.

Noting its rulings of no breaches of Clauses 6.1 and 6.2 of the Code above, the Panel did not consider that the complainant had demonstrated that AbbVie had failed to maintain high standards and ruled **no breach of Clause 5.1** of the Code. The Panel consequently ruled **no breach of Clause 2**.

Complaint received **14 November 2022**

Case completed **20 November 2023**