CASE AUTH/3321/3/20

COMPLAINANT v A MENARINI

Disguised promotion of Ranexa

A complainant, who described him/herself as a concerned UK health professional, complained that material, hosted on the Guidelines in Practice website and produced by A Menarini, was disguised promotion for Ranexa (ranolazine). Ranexa was indicated in certain adults as add-on therapy for the symptomatic treatment of stable angina.

The complainant drew specific attention to a webpage which presented a supplement entitled 'Delivering savings by improving the management of patients with chronic coronary syndrome in the [acute medical unit] setting: a case study' (Ako and Smith 2019). The complainant stated that he/she did not realise that the supplement was a promotional item until he/she noticed there was a link to prescribing information; the same was true for the downloadable copy of the supplement which contained prescribing information at the back of the item. The complainant alleged that both the on-line and downloadable items were disguised promotion.

The complainant further noted, with regard to patient safety, that the prescribing information was from 2017 and that updates had included special warnings on QT prolongation which was extremely relevant to the those who would be treated with Ranexa. Given that the material was created in 2019, the complainant queried whether the company's review process was sufficiently robust.

The detailed response from A Menarini is given below.

The Panel noted that, at the outset, the online material included a statement that it had been commissioned and funded by A Menarini with a more detailed description of the company's involvement at the end of the piece. Readers' attention was also drawn, at the outset, to a link to prescribing information. In the Panel's view, health professionals visiting the webpage at issue would be immediately aware that the material was developed by A Menarini and would be likely to assume that it would include information on A Menarini's medicines and therefore be promotional. The Panel did not consider that the promotional nature of the on-line material had been disguised. No breach was ruled.

The downloadable copy of the material did not state at the outset that the material had been commissioned and funded by A Menarini. The Panel noted A Menarini's submission that it would have been helpful to have an additional statement of its involvement at the top of the front page and it would ensure that that was the case for future such materials. That the company had any involvement in the piece at issue was only noted in a footnote at the bottom of the front page along with directions as to where to find the prescribing information. The Panel accepted that a health professional downloading the PDF copy from the website would have done so knowing that the piece was promotional. In the Panel's view, however, the hard copy had to be capable of

standing alone with regard to the requirements of the Code. Given that the company's involvement was not immediately obvious on the printed material, the Panel considered that its promotional nature had been disguised. A breach of the Code was ruled.

The Panel noted A Menarini's submission that in November 2018 Section 4.4, Special warnings and precautions for use, of the Ranexa summary of product characteristics (SPC) was updated to include the following:

> **'QT prolongation: Ranolazine blocks I_{Kr} and prolongs the QTc interval in a dose-related manner.'**

The rest of the information related to the QT prolongation in Section 4.4 remained the same as the previous version dated 15 December 2016:

> **'A population-based analysis of combined data from patients and healthy volunteers demonstrated that the slope of the plasma concentration-QTc relationship was estimated to be 2.4msec per 1000ng/ml, which is approximately equal to a 2- to 7-msec increase over the plasma concentration range for ranolazine 500 to 1000mg twice daily. Therefore, caution should be observed when treating patients with a history of congenital or a family history of long QT syndrome, in patients with known acquired QT interval prolongation, and in patients treated with drugs affecting the QTc interval (see section 4.5 also).'**

The Panel noted that the prescribing information at issue, produced in January 2017 and reapproved in February 2019, stated in the Warnings and Precautions section that for QT prolongation, caution should be observed when treating patients with a history of congenital or a family history of long QT syndrome, in patients with known acquired QT interval prolongation, and in patients treated with drugs affecting the QTc interval. In the Panel's view, the statement added to the November 2018 SPC did not materially affect the succinct warning required in the prescribing information. Readers were advised to consult the SPC for full prescribing information and in doing so they would discover the reasons behind the warning. The Panel noted that the complainant had not stated why he/she considered that the issue was a matter of patient safety and in that regard considered that he/she had not discharged the burden of proving his/her complaint on the balance of probabilities. On the information before it, the Panel did not consider that the prescribing information was inadequate with regard to the warning given about QTc interval prolongation. No breach of the Code was ruled.

The Panel noted its comments and rulings above and considered that, in the particular circumstances of this case, A Menarini had not failed to maintain high standards and no breach of the Code was ruled including no breach of Clause 2.

A complainant, who described him/herself as a concerned UK health professional, complained that material produced by A Menarini, which had been hosted on the website of the journal Guidelines in Practice, was disguised promotion for Ranexa (ranolazine). Ranexa was indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who were inadequately controlled or intolerant to first-line anti-anginal therapies (such as beta-blockers and/or calcium antagonists).

COMPLAINT

The complainant drew attention to the website of the journal Guidelines in Practice (www.guidelinesinpractice.co.uk) and specifically to a page which presented a supplement entitled 'Delivering savings by improving the management of patients with chronic coronary syndrome in the [acute medical unit] setting: a case study' (Ako and Smith 2019). The complainant stated that he/she did not realise that the supplement was a promotional item until he/she noticed there was a link to prescribing information. The complainant stated that the same was true for the downloadable copy of the supplement which contained prescribing information at the back of the item. The complainant alleged that both the on-line and downloadable items were disguised promotion.

The complainant further noted that the prescribing information was from 2017 and that there had been three updates including special warnings on QT prolongation which was extremely relevant to the patients who would be treated with Ranexa and so this was a matter of patient safety. Given that the material was created in 2019, the complainant queried whether the company's review process was sufficiently robust.

When writing to A Menarini, the Authority asked it to consider the requirements of Clauses 4.1, 9.1, 12.1 and 2 of the Code.

RESPONSE

A Menarini explained that the case study in question demonstrated that improving the management of patients with chronic coronary syndrome in the acute medical unit setting could lead to financial savings to the healthcare system. The material was intended to be used by health professionals involved in the management of chronic coronary syndrome in acute medical units and it provided them suggested guidance through a real-life case study.

A Menarini explained that the study was commissioned and funded by A Menarini Farmaceutica Internazionale S.r.l. The UK company, however, suggested the topic and authors and had developed the piece in partnership with Guidelines in Practice. The UK carried out a full medical approval on all materials to ensure compliance with UK regulations before the material was placed on the Guidelines in Practice website on 7 November 2019.

A Menarini provided a screenshot of the material at issue and noted that, immediately beneath the title, it was clearly labelled as being commissioned by A Menarini. Immediately beneath the author's names, and immediately to the right of the PDF icon, there was a further statement that the document had been commissioned by A Menarini; readers were immediately directed to a full statement about A Menarini's involvement at the foot of the page. Immediately beneath that, and also next to the PDF icon, there was a clear and prominent link to 'prescribing information'.

A Menarini noted the complainant's comment that he/she did not realise the item was promotional until he/she noticed the link to prescribing information. A Menarini submitted that when the complainant saw the link to prescribing information he/she had not accessed the actual material and so no promotion could possibly have occurred. The article was available by scrolling down the screen or from downloading the PDF.

A Menarini stated that as the PDF itself was accessed from the webpage, it was hard to see how readers could open the PDF without realising A Menarini's involvement unless they deliberately ignored the obvious and prominent declarations of the company's involvement. A

Menarini noted that although the webpage did not explicitly state that the material was promotional, there was no requirement in the Code to do so; only that promotional material and activities must not be disguised (Clause 12.1).

The supplementary information to Clause 12.1 stated that 'When a company pays for, or otherwise secures or arranges the publication of promotional material in journals, such material must not resemble independent editorial matter'. A Menarini noted that, in addition to bearing clear adjacent statements that the company had commissioned the document, and direction to a full description of its involvement, the page did not bear the icon indicating independent content, with which readers of Guidelines in Practice were familiar.

A Menarini did not accept that the downloadable PDF was disguised promotion given that access to it was juxtaposed next to statements of the company's involvement and also the link to prescribing information (as indicated above). Further, the bottom of the front page of the PDF bore a very detailed statement about the nature of the company's involvement. A Menarini recognised that it would have been helpful to have an additional statement of its involvement at the top of the front page and it would ensure that that was the case for future such materials. However, the first mention of Ranexa was in the flow chart on page 2; after the declaration of the company's involvement on the front page.

A Menarini categorically denied any breach of Clause 12.1 for disguised promotion in relation to the website or PDF versions of the material.

A Menarini noted that Clause 4.1 required the prescribing information listed in Clause 4.2 to be provided in a clear and legible manner in all promotional material for a medicine except for abbreviated advertisements. A Menarini noted that a clear and prominent link to prescribing information was juxtaposed to the PDF and before the reader could scroll down to the web-based version of the article. The prescribing information was also on the back page of the PDF and a clear signpost to the back page was included on the front page of the PDF. In that way, the prescribing information formed part of the promotional material as required by the Code and was not separated from it.

A Menarini submitted that the prescribing information was consistent with the summary of product characteristics (SPC) updated 22 November 2018 and last updated 28 March 2019. The November 2018 SPC included the following update in Section 4.4, Special warnings and precautions for use:

> 'QT prolongation: Ranolazine blocks I_{Kr} and prolongs the QTc interval in a dose-related manner.'

The rest of the information related to the QT prolongation in Section 4.4 remained the same as the previous version dated 15 December 2016:

> 'A population-based analysis of combined data from patients and healthy volunteers demonstrated that the slope of the plasma concentration-QTc relationship was estimated to be 2.4msec per 1000ng/ml, which is approximately equal to a 2- to 7-msec increase over the plasma concentration range for ranolazine 500 to 1000mg twice daily. Therefore, caution should be observed when treating patients with a history of congenital or a family history of long QT syndrome, in patients with known acquired QT interval prolongation, and in patients treated with drugs affecting the QTc interval (see section 4.5 also).'

The prescribing information produced in January 2017 and reapproved in February 2019 contained the following:

> '**Warnings and Precautions**: Caution should be exercised when prescribing or up titrating ranolazine to patients in whom an increased exposure is expected. QT prolongation: Caution should be observed when treating patients with a history of congenital or a family history of long QT syndrome, in patients with known acquired QT interval prolongation, and in patients treated with drugs affecting the QTc interval.'

A Menarini submitted that the update 'Ranolazine blocks I_{Kr} and prolongs the QTc interval in a dose-related manner' did not add any significant information regarding the use of ranolazine in this subgroup of patients. The company thus denied a breach of Clause 4.1.

A Menarini stated that the material was created, reviewed and published in line with established company and supplier processes. It was clearly labelled as being commissioned by the company and clear and current prescribing information was provided. High standards were clearly maintained.

The company considered that the publishing of the case study involving cardiac patients in the acute medical unit setting was beneficial not only to the NHS in terms of patient care but also potential financial savings to the healthcare system. The authors of the article and the acute medical unit at the relevant NHS Foundation Trust also received a national award for excellence in patient care for the acute medical unit/cardiology collaboration to improve patient care in stable angina chest pain management. The company's support in developing the supplement in question had given other parts of the NHS an opportunity to learn from some real-life best practice.

A Menarini thus categorically denied any breaches of Clause 9.1 or 2.

PANEL RULING

The Panel noted that promotional material did not need to be labelled as such, however, it must not be disguised, and should otherwise comply with the Code. The Panel noted that, at the outset, the online material included a statement that it had been commissioned and funded by A Menarini with a more detailed description of the company's involvement at the end of the piece. Readers' attention was also drawn, at the outset, to a link to prescribing information. In the Panel's view, health professionals visiting the webpage at issue would be immediately aware that the material was developed by A Menarini and, on the balance of probabilities, would be likely to assume that it would include material on A Menarini's medicines and therefore be promotional. The Panel did not consider that the promotional nature of the on-line material had been disguised. No breach of Clause 12.1 was ruled.

The downloadable copy of the material did not state at the outset that the material had been commissioned and funded by A Menarini. The Panel noted A Menarini's submission that it would have been helpful to have an additional statement of its involvement at the top of the front page and it would ensure that that was the case for future such materials. That the company had any involvement in the piece at issue was only noted in a footnote at the bottom of the front page along with directions as to where to find the prescribing information. The Panel accepted that if a health professional had downloaded the PDF copy from the website then he/she would

have done so knowing that the piece was promotional. In the Panel's view, however, the hard copy had to be capable of standing alone with regard to the requirements of the Code. Given that the company's involvement was not immediately obvious on the printed material, the Panel considered that its promotional nature had been disguised. A breach of Clause 12.1 was ruled.

The Panel noted A Menarini's submission that in November 2018 Section 4.4, Special warnings and precautions for use, of the Ranexa SPC was updated to include the following:

> 'QT prolongation: Ranolazine blocks I_{Kr} and prolongs the QTc interval in a dose-related manner.'

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The Panel noted its comments and rulings above and considered that, in the particular circumstances of this case, A Menarini had not failed to maintain high standards and no breach of Clause 9.1 was ruled.

The Panel noted its rulings above and 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 a ruling of a breach of Clause 2 was warranted in this case. No breach was ruled.

Complaint received **10 March 2020**

Case completed **2 June 2020**