CASE AUTH/3239/8/19

PHARMACIST v COLONIS

Promotion of Melatonin Oral Solution

A pharmacist in a medicines optimisation team, complained that in a letter (ref UK-CPL-121-008), Colonis Pharma Limited had blatantly promoted off-label use of Melatonin 1mg/ml Oral Solution. The medicine was only indicated for the short-term treatment of jet-lag in adults but there was hardly any reference to that in the letter.

The detailed response from Colonis is given below.

The Panel noted that the licensed indication for Melatonin 1mg/ml Oral Solution, 'for short-term treatment of jet-lag in adults', was stated in bold black, regular sized font in the first sentence of the letter. This was the only refence to the licensed indication in the letter which mainly otherwise discussed the use of the medicine in preference to unlicensed alternatives.

The Panel noted that it was not necessarily unacceptable to draw the attention of pharmacists, medicines optimisation teams and CCG medicines management teams to the relevant legal requirements about the use of unlicensed medicines, however such material had to comply with the Code.

The Panel noted that the Melatonin 1mg/ml Oral Solution summary of product characteristics (SPC) stated that the safety and efficacy of the medicine in children and adolescents aged 0-18 years had not been established and that Melatonin 1mg/ml Oral Solution should not be used in children and adolescents due to safety and efficacy concerns.

The Panel further noted that the letter highlighted that Melatonin 1mg/ml Oral Solution was lactose free, sugar free and strawberry flavoured. Directly beneath these statements was the question, 'Why choose a liquid formulation?'; the answers included 'Can be used over a wide age range'. Both the product characteristics noted above and answers were in capital letters in prominent coloured circles, in a larger font size than that used to state the licensed indication.

The Panel noted that the letter stated, in larger font than that used to set out the indication for use, that Melatonin 1mg/ml Oral Solution was now licensed and that it should be prescribed over unlicensed alternatives. A schematic which ranked options from 'low risk' to 'high risk', placed UK licensed medicines used off-label at the low risk (green) end of the spectrum, second only to a UK licensed medicine. The Panel considered that off-label use of Melatonin 1mg/ml Oral Solution might include use in many different patient types including children and adolescents and in this regard the Panel noted its comments above in relation to the statement in the letter 'Can be used over a wide age range'. The Panel considered the immediate and overall impression to a

health professional. In the Panel's view, the letter promoted Melatonin 1mg/ml Oral Solution for off-label use and a breach of the Code was ruled.

The Panel considered that patient safety had been compromised by the promotion of off-label use, compounded by the lack of any warning to alert the reader, *inter alia*, that Melatonin 1mg/ml Oral Solution should not be used in children and adolescents. A breach of was ruled as high standards had not been maintained.

The Panel noted that a ruling of a breach of Clause 2 was reserved as a sign of particular censure. The supplementary information to Clause 2 gave examples of activities likely to be in breach of Clause 2 which included prejudicing patient safety. The Panel noted its comments and rulings above and considered that the letter brought discredit upon, and reduced confidence in, the pharmaceutical industry and ruled a breach of Clause 2.

A pharmacist in the medicines optimisation team at a university NHS foundation trust, complained about a letter (ref UK-CPL-121-008) promoting Melatonin 1mg/ml Oral Solution sent by Colonis Pharma Limited. Melatonin 1mg/ml Oral Solution was indicated for the short-term treatment of jet-lag in adults.

COMPLAINT

The complainant stated that he/she was shocked by how blatantly Colonis had promoted off-label use of a licensed medicine. The letter made hardly any reference to the licensed indication for the new product.

When writing to Colonis, the Authority asked it to consider the requirements of Clauses 3.2, 9.1 and 2.

RESPONSE

Colonis explained that the one-off letter at issue was posted to 18,649 hospital pharmacists, procurement pharmacists, medicine optimisation teams and clinical commissioning group (CCG) medicines management teams on 25 June 2019 as a launch notification for Melatonin 1mg/ml Oral Solution. The mailing announced the availability of the licensed product for use in short-term treatment of jet-lag in adults.

Colonis did not consider that the letter promoted the off-label use of its medicine particularly as it was clearly stated in the opening paragraph that 'This letter is to inform you that Melatonin 1mg/ml Oral Solution has recently been granted a licensed indication for short-term treatment of jet-lag in adults'.

Colonis submitted that the intention was to simply state that the newly licensed product could be used for short-term treatment of jet-lag in adults and that it should be used instead of unlicensed alternatives ('specials') of the same strength and presentation, so long as it met the patient's clinical needs.

Colonis submitted that within the letter the emboldened statement 'Melatonin 1mg/ml Oral Solution should be prescribed over unlicensed alternatives' and the 'Hierarchy of risk for unlicensed medicines' emboldened depiction were consistent with guidance from the Medicines and Healthcare products Regulatory Authority (MHRA) regarding the supply of unlicensed

medicinal products ((specials) Guidance Note 14). The guidance stated that 'An unlicensed medicinal product may only be supplied in order to meet the special needs of an individual patient. An unlicensed medicinal product should not be supplied where an equivalent licensed medicinal product can meet the special needs of the patient'.

Colonis submitted that as further clarification to the statement above, it was also stated in the letter that 'If there is a genuine clinical need, licensed products should be used off-label instead of unlicensed alternatives.' This was consistent with MHRA guidance which stated 'Although MHRA does not recommend "off-label" (outside the licensed indications) use of products, if a UK licensed product can meet the clinical need, even off-label, it should be used instead of an unlicensed product'.

Colonis stated that, in a complex prescribing area, the mailing sought to bring to pharmacists' and purchasers' attention the availability of its licensed product and the approved indication. In addition, the company was mindful of the considerable prescribing, manufacture and supply of unlicensed 'specials' presentations of melatonin Oral Solution. By referring to the prescribing hierarchy as outlined in MHRA guidance, Colonis wished to advise pharmacists and purchasers as to where its licensed product would fit into the hierarchy and what steps they might need to take if they currently supplied an unlicensed 'special'.

Colonis stated that it never intended to promote off-label use, but simply to note that MHRA guidance stated that should it meet a patient's clinical need a UK licensed product used off-label represented less risk to the patient and should be used in preference to the unlicensed 'special'.

Colonis submitted that the letter did not target prescribing use as it was not sent to clinician prescribers; it was sent to purchasers to make them aware of the availability of the product.

Colonis stated that, in the interim, the MHRA had received several complaints alleging that the letter appeared to promote off-label use of the product, including use in children. The intention had never been to promote Melatonin for off-label use, not least in children, and so following correspondence with the MHRA, Colonis sent an agreed corrective letter (copy provided) to those who had received the original letter. The corrective letter (dated 24 July 2019) clarified the licensed indication and safety restrictions for use in certain populations (eg paediatric population – should not be used in children and adolescents aged 0-18 years due to efficacy and safety concerns) and included a copy of the summary of product characteristics (SPC).

Colonis stated that it hoped that it was clear that the letter was intended to announce the availability of the new product for its licensed indication, and that it should be used over unlicensed products as per MHRA Guidance Note 14. Colonis submitted that, in its view, it had achieved this without giving the appearance of promoting off-label use, notwithstanding the MHRA Guidance Note 14 permitting (but not actually recommending) off-label use if the clinical need could be met instead of an unlicensed product. Consequently, Colonis did not consider that it had promoted the off-label use of Melatonin and therefore it denied a breach of Clause 3.2.

Colonis stated that it considered that it had not breached Clause 3.2 and that in liaison with the MHRA it took timely and appropriate action to issue an agreed corrective letter to clarify the licensed indication and safety restrictions; it considered that it had responsibly addressed any possible suggestions of off-label use and associated safety concerns and had therefore maintained high standards. Consequently, Colonis denied a breach of Clause 9.1.

Colonis submitted that as, in its view, it was not in breach of Clause 3.2 or 9.1, it would be inappropriate to rule a breach of Clause 2, specifically as it considered that the actions the company took to avoid prejudicing patient safety were appropriate and that Colonis had not been involved with any potential Code breaches prior to this mailing.

PANEL RULING

The Panel noted that the licensed indication for Melatonin 1mg/ml Oral Solution 'for short-term treatment of jet-lag in adults' was stated in bold black, regular sized font in the first sentence of the letter. This was the only refence to the licensed indication in the letter which mainly otherwise discussed the use of Melatonin 1mg/ml Oral Solution in preference to unlicensed alternatives. The Panel noted that the incorrect prescribing information was supplied with the letter at issue; the prescribing information supplied related to Melatonin 3mg film-coated tablets, however the letter promoted Melatonin 1mg/ml Oral Solution.

The Panel noted that it was not necessarily unacceptable to draw the attention of pharmacists, medicines optimisation teams and CCG medicines management teams to the relevant legal requirements about the use of unlicensed medicines, however such material had to comply with the Code.

The Panel noted that the Melatonin 1mg/ml Oral Solution SPC stated in Sections 4.2 'Posology and method of administration' and 4.4 'Special warnings and precautions for use' that the safety and efficacy of the medicine in children and adolescents aged 0-18 years had not been established and that Melatonin 1mg/ml Oral Solution should not be used in children and adolescents due to safety and efficacy concerns. Section 5.1 of the SPC gave further details in this regard.

The Panel further noted that the letter highlighted Melatonin 1mg/ml Oral Solution's product characteristics as being lactose free, sugar free and strawberry flavouring. Directly beneath these statements was the question, 'Why choose a liquid formulation?'; the answers included 'Can be used over a wide age range'. Both the product characteristics and answers were in capital letters in prominent coloured circles, in a larger font size than that used to state the licensed indication 'for short-term treatment of jet-lag in adults'.

The Panel noted that the letter stated, in larger font than that used to set out the indication for use, that Melatonin 1mg/ml Oral Solution was now licensed and that it should be prescribed over unlicensed alternatives. A schematic which ranked options from 'low risk' to 'high risk', with colours changing from green (low risk) to red (high risk) placed UK licensed medicines used off-label at the low risk (green) end of the spectrum, second only to a UK licensed medicine. The Panel considered that off-label use of Melatonin 1mg/ml Oral Solution might include use in many different patient types including children and adolescents and in this regard the Panel noted its comments above in relation to the statement in the letter 'Can be used over a wide age range'. The Panel considered the immediate and overall impression to a health professional. In the Panel's view, the letter promoted Melatonin 1mg/ml Oral Solution for off-label use and a breach of Clause 3.2 was ruled.

The Panel considered that patient safety had been compromised by the promotion of off-label use, compounded by the lack of any warning to alert the reader, *inter alia*, that Melatonin

1mg/ml Oral Solution should not be used in children and adolescents due to safety and efficacy concerns. 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 was reserved for such use. The supplementary information to Clause 2 gave examples of activities likely to be in breach of Clause 2 which included prejudicing patient safety. The Panel noted its comments and rulings above and considered that the letter brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

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During the consideration of this case, the Panel noted that the corrective letter which the MHRA asked Colonis to send to those in receipt of the original letter stated, '… the reference used in the original mailing citing [a named] CCG was in no way intended to suggest they had endorsed our product, which they do not. We wish to apologise to [the named] CCG for referring to their document without their express permission …'. The Panel noted that Colonis' submission to Case AUTH/3221/6/19 did not include that Colonis had not obtained the appropriate permissions from [the named] CCG to cite the CCG in the company's promotional letter. Self-regulation relied on complete and accurate responses from companies.

Complaint received **13 August 2019**

Case completed **20 December 2019**