CASE AUTH/3240/8/19

VOLUNTARY ADMISSION FROM COLONIS

Incorrect prescribing information

Colonis Pharma Limited voluntarily admitted that it had included the wrong prescribing information in a promotional letter (ref UK-CPL-121-008) about Melatonin 1mg/ml Oral Solution which was indicated for the short-term treatment of jet-lag in adults.

As Paragraph 5.5 of the Constitution and Procedure required the Director to treat a voluntary admission as a complaint, the matter was taken up with Colonis.

The detailed response from Colonis is given below.

The Panel noted that the letter in question promoted Melatonin 1mg/ml Oral Solution but the prescribing information provided was that for Melatonin 3mg film-coated tablets. In that regard, the relevant prescribing information had not been provided as required by the Code. A breach of the Code was ruled.

The incorrect prescribing information in the letter was not identified by Colonis at either the final internal hard copy print sign-off stage or the external printer QC and dispatch stage. Colonis had failed to maintain high standards and a breach of was ruled.

The Panel noted Colonis' submission that although the letter contained the incorrect prescribing information, the risk to patient safety was low as the main safety information was consistent for both the tablet formulation and the Oral Solution.

The Panel noted that there were differences in the summary of product characteristics (SPC) between the Oral Solution and the film-coated tablets that would impact the prescribing information.

The Panel was concerned that important safety information relating to the Oral Solution was not provided by virtue of the fact that the film-coated tablets prescribing information was supplied in error.

The Panel noted its comments and rulings above and was concerned that the error had not been picked up during two different stages of the approvals process. The approvals process underpinned self- regulation and any failure in that regard was a serious matter. Clause 2 was a sign of particular censure and was reserved for such use. The supplementary information to this clause listed activities likely to be found in breach of Clause 2 and included prejudicing patient safety. The Panel considered that the provision of incorrect prescribing information which omitted important safety information meant that Colonis had brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

Colonis provided the requisite undertaking and assurance and as the case completed at Panel level the Appeal Board received the case report as set out in Paragraph 13.4 of the Constitution and Procedure.

The Appeal Board noted the Panel's comments regarding Colonis' submission that it had sent a corrective letter on 23 July to the recipients of the original letter to point out and apologise for the oversight in relation to the incorrect prescribing information. There had been no mention in this case that the corrective letter had been a corrective statement required and agreed by the MHRA as advised by Colonis in its submission to Case AUTH/3239/8/19. The Panel queried why Colonis' submission in Case AUTH/3240/8/19 did not refer to the company's correspondence with the MHRA and it noted that self-regulation relied on complete and accurate responses from companies.

The Appeal Board was concerned about the incomplete and inaccurate responses and it was of the view that consideration should be given to the imposition of additional sanctions under Paragraph 11.1 of the Constitution and Procedure. Colonis should respond to these concerns in writing and it was invited to attend the Appeal Board when this matter was considered.

The detailed response from Colonis to the possibility of further sanctions being imposed is given below.

The Appeal Board noted the Panel's rulings of breaches of the Code including Clause 2. The Appeal Board noted that the company had apologised and admitted that it had made errors. The company submitted that these were administrative errors due to its unfamiliarity with the complaints procedure and a lack of understanding of the importance or relevance of the information which should have been provided. The Appeal Board noted that Colonis had failed to state in its response to Case AUTH/3240/8/19 that the corrective letter on 23 July was required by the MHRA. Although the response to Case AUTH/3239/8/19 included a copy of the corrective statement in question the company's letter should have been clearer that the MHRA required a corrective statement to be sent. The information included in Case AUTH/3239/8/19 was clearly relevant to the current case, Case AUTH/3240/8/19. Both responses had been sent to the Authority by Colonis on the same day. The Appeal Board noted that any case under the Code must stand alone and be considered on its individual merits. Case AUTH/3239/8/19 and Case AUTH/3240/8/19 had not been amalgamated under Paragraph 5.1 of the Constitution and Procedure. It was essential that companies had an in depth understanding of the Code and the Constitution and Procedure including responding to complaints. The Appeal Board noted that self-regulation relied, inter alia, upon the provision of complete and accurate information from pharmaceutical companies.

The Appeal Board noted Colonis' submission that it was a subsidiary of Clinigen set up to develop and bring to market products that were currently used as specials. The Appeal Board noted the area in which Colonis was working in and the apparent lack of Code knowledge which was of concern. The Appeal Board noted, however, that the company was in the process of being fully integrated into Clinigen which should bring increased compliance resource and oversight.

The Appeal Board decided that, in accordance with Paragraph 11.3 of the Constitution and Procedure, Colonis should be publicly reprimanded for its failure to provide complete and accurate information to the Panel.

The Appeal Board gave consideration to the use of further sanctions but decided that, on balance, none were required.

Colonis Pharma Limited voluntarily admitted that it had included the wrong prescribing information in a promotional letter (ref UK-CPL-121-008) about Melatonin 1mg/ml Oral Solution which was indicated for the short-term treatment of jet-lag in adults.

As Paragraph 5.5 of the Constitution and Procedure required the Director to treat a voluntary admission as a complaint, the matter was taken up with Colonis.

VOLUNTARY ADMISSION

As a result of investigating a complaint about the letter (Case AUTH/3221/6/19), Colonis realised that the prescribing information headed 'Melatonin 1mg/ml Oral Solution' actually contained the text relating to the Melatonin 3mg Film-Coated Tablets. Although the company considered that the risk to patient safety was low, it was very concerned about this occurrence and investigated how it happened. It appeared that the error was picked up and corrected during the early approval round, but recurred and was overlooked at the final internal hard copy print proof sign-off stage and also at the printer QC and dispatch stages. Colonis stated that it had since taken remedial steps within its copy review approvals system, based on its CAPA process, to prevent such an error from happening in the future. However, in respect of further immediate actions being taken for those in receipt of the original letter, the company had sent a corrective letter with the Melatonin 1mg/ml Oral Solution summary of product characteristics (SPC), and had noted and apologised for the oversight. Colonis acknowledged that its approvals system had fallen short of the high standards that the business would normally expect. The company, however, considered that it had taken appropriate and immediate corrective actions to ensure that it did not recur. Given the nature of the oversight, Colonis considered that the Panel should consider a breach of Clause 4.1.

When writing to Colonis, the Authority asked it to consider the requirements of Clauses 2 and 9.1 in addition to Clause 4.1 cited by the company.

RESPONSE

Colonis reiterated that it was very concerned that the incorrect prescribing information had been used, particularly in relation to there being any potential risk to patient safety and immediately consulted its pharmacovigilance department. The pharmacovigilance department reviewed the oversight and considered that the risk to patient safety was low as the main safety information was consistent across both product formulations, the letter was not sent to clinician prescribers and the SPC rather than the prescribing information should be used for actual prescribing and it clearly stated under the heading 'Prescribing Information', 'Please refer to Summary of Product Characteristics (SmPC) before prescribing'. Colonis submitted that it immediately formally withdrew the single use letter and investigated how the error had occurred. Colonis submitted that the error was picked up and corrected during the early internal approval round, but recurred and was overlooked at the final internal hard copy print proof sign-off stage and also at the external printer QC and dispatch stages.

In addition, on 23 July 2019 the company sent a corrective letter which contained the Melatonin 1mg/ml Oral Solution SPC to those sent the original letter and it noted and apologised for the oversight.

Colonis submitted that as a result of the company's internal investigation, it had improved its working practices around the internal copy review approvals procedure and reviewed its interactions with outside agencies to prevent such an error from happening in the future.

As stated above, the oversight showed a shortcoming in carrying out the copy review approvals procedure and that its working practices had fallen short of the high standards that the company would expect to uphold in conducting its business.

Colonis considered that it had shown that it carefully considered the oversight, particularly bearing in mind any patient safety risks, and took appropriate and timely corrective actions to ensure that any risk to patient safety was minimised and that this oversight did not recur. However, given the nature of the oversight, the company acknowledged a breach of Clause 4.1.

With regard to Clause 9.1, Colonis submitted that in outlining its consideration of the oversight, particularly in respect of any possible risk to patient safety, and its subsequent timely investigative and corrective actions to this, it considered that it had demonstrated an appropriate and responsible response to the issue. However, in respect of the shortcomings shown in its copy review approvals procedure, the company considered that it had failed to maintain high standards and had consequently breached Clause 9.1.

Although the company acknowledged breaches of Clauses 4.1 and 9.1 in respect of shortcomings in its copy review approvals procedure, it had otherwise shown by its timely response and corrective actions that it had responded correctly and responsibly to the issue. Consequently, Colonis considered that in this particular case it would be inappropriate to rule a breach of Clause 2, specifically as Colonis considered that the steps it took to avoid prejudicing patient safety were appropriate and it had not been involved with any potential Code breaches prior to the letter being sent out.

PANEL RULING

The Panel noted that the letter in question promoted Melatonin 1mg/ml Oral Solution but the prescribing information provided was that for Melatonin 3mg film-coated tablets. In that regard the relevant prescribing information had not been provided as required by the Code. A breach of Clause 4.1 was ruled.

The incorrect prescribing information in the letter was not identified by Colonis at either the final internal hard copy print sign-off stage or the external printer QC and dispatch stage. Colonis had failed to maintain high standards and a breach of Clause 9.1 was ruled.

The Panel noted Colonis' submission that although the letter contained the incorrect prescribing information, the risk to patient safety was low as the main safety information was consistent for both the tablet formulation and the Oral Solution.

The Panel noted that there were differences in the summary of product characteristics (SPC) between the Oral Solution and the film-coated tablets that would impact the prescribing information.

Of particular note, Section 4.4 'Special warnings and precautions for use' of the Melatonin 1mg/ml Oral Solution SPC stated in bold, 'Melatonin 1mg/ml Oral Solution contains sorbitol, ethanol and propylene glycol'. It further stated:

> 'This medicinal product contains sorbitol. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.'

The Melatonin 3mg film-coated tablets prescribing information, which was incorrectly supplied with the letter at issue, stated under Warnings and precautions 'the tablets contain lactose, thus not recommended in patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption'.

The Panel was therefore concerned that important safety information relating to the Oral Solution, which the letter in question promoted, was not provided by virtue of the fact that the film-coated tablets prescribing information was supplied in error.

The Panel disagreed with Colonis' submission that as the SPC rather than the prescribing information should be used for prescribing, and the letter was not sent to clinician prescribers, that the risk to patient safety was low. Such a submission undermined the importance of prescribing information and its use in all promotional material regardless of whether the recipient was a prescriber.

The Panel noted its comments and rulings above and was concerned that the error had not been picked up during two different stages of the approvals process. The approvals process underpinned self- regulation and any failure in that regard was a serious matter. Clause 2 was a sign of particular censure and was reserved for such use. The supplementary information to this clause listed activities likely to be found in breach of Clause 2 and included prejudicing patient safety. The Panel considered that the provision of incorrect prescribing information which omitted important safety information related to the medicine which the material promoted meant that Colonis had brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

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During its consideration of this case, the Panel noted Colonis' submission that the company sent a corrective letter on 23 July to the recipients of the original letter to point out and apologise for the oversight in relation to the incorrect prescribing information. Colonis' submission made no reference to the MHRA in this regard. However, the Panel noted that Colonis' submission to Case AUTH/3239/8/19 stated that the company had received a letter from the MHRA stating that they had been in receipt of several complaints in relation to off-label promotion and following correspondence with the MHRA 'we sent an agreed corrective mailing'. The corrective mailing, dated 24 July, stated 'The MHRA have asked Colonis Pharma to provide a corrective statement …'. The Panel noted that this corrective statement referred to a number of issues with the original promotional letter including the provision of incorrect prescribing information. The Panel queried why Colonis in Case AUTH/3240/8/19 did not refer to the company's correspondence with the MHRA in this regard. Self-regulation relied on complete and accurate responses from companies.

APPEAL BOARD CONSIDERATION OF CASE REPORT

Colonis provided the requisite undertaking and assurance and as the case completed at Panel level the Appeal Board received the case report as set out in Paragraph 13.4 of the Constitution and Procedure.

The Appeal Board noted the Panel's comments regarding Colonis' submission that it had sent a corrective letter on 23 July to the recipients of the original letter to point out and apologise for the oversight in relation to the incorrect prescribing information. There had been no mention in this case that this had been a corrective statement required and agreed by the MHRA as advised by Colonis in its submission to Case AUTH/3239/8/19 (above). The Panel queried why Colonis' submission in Case AUTH/3240/8/19 did not refer to the company's correspondence with the MHRA and it noted that self-regulation relied on complete and accurate responses from companies.

The Appeal Board was concerned about the incomplete and inaccurate responses and it was of the view that consideration should be given to the imposition of additional sanctions under Paragraph 11.1 of the Constitution and Procedure. Colonis should respond to these concerns in writing and it was invited to attend the Appeal Board when this matter was considered. Colonis was provided with a copy of the papers.

COMMENTS FROM COLONIS

Colonis noted that the Appeal Board had concerns that its response to the above complaint had been incomplete and inaccurate, specifically that it did not mention in its response that the corrective mailing sent on 23 July 2019 to recipients of the original mailing had been required and agreed by the MHRA as advised by Colonis in its submission to Case AUTH/3239/8/19.

Colonis submitted that the Appeal Board would be aware that it had several complaints relating to this single mailing which was a launch notification for Melatonin 1mg/ml Oral Solution. Two were received directly via the PMCPA, namely: Case AUTH/3221/6/19 – letter dated 28 June 2019 and Case AUTH/3239/8/19 – letter dated 15 August 2019 and a third from the PMCPA as a result of its voluntary admission about the incorrect prescribing information, Case AUTH/3240/8/19 – letter dated 15 August 2019.

Colonis submitted that on the 10 July 2019 it also received a letter from an Assessor at the Advertising Standards & Outreach Unit at the MHRA, informing it that the MHRA had also received several complaints about the mailing alleging off-label promotion and the MHRA also drew attention to the fact that the mailing contained the prescribing information for Melatonin 3mg Film-Coated Tablets and not the Oral Solution.

Colonis submitted that following correspondence with the MHRA, the wording for the corrective mailing was agreed and was sent on 23 July 2019 which clarified the licensed indication and safety restrictions for use in certain patient populations. The mailing also drew recipients' attention to the error in the prescribing information and provided a copy of the SPC for Melatonin 1mg/ml Oral Solution.

Colonis submitted that in its response to the PMCPA to Case AUTH/3221/6/19 dated 11 July 2019 it included the voluntary admission in relation to the incorrect prescribing information, which became Case AUTH/3240/8/19 and as stated above this was dated 15 August 2019, the same date as Case AUTH/3239/8/19. In its response to Case AUTH/3239/8/19 on 30 August 2019 Colonis advised the PMCPA as follows:

> 'As our intention was never to promote Melatonin for off-label use, not least in children, following correspondence with the MHRA we sent an agreed corrective mailing (enclosed) to those in receipt of the original letter, attaching the Melatonin 1mg/ml Oral Solution Summary of Product Characteristics (SmPC), clarifying the licensed indication and safety restrictions for use in certain populations (e.g. Paediatric population – should not be used in children and adolescents aged 0-18 years due to efficacy and safety concerns).'

Colonis submitted that, as indicated, it also enclosed a copy of the corrective mailing with its response. In response to Case AUTH/3240/8/19, also on 30 August 2019, Colonis advised the PMCPA as follows:

> 'In addition, on 23 July 2019 we sent a corrective mailing containing the Melatonin 1mg/ml Oral Solution Summary of Product Characteristics (SmPC) to those sent the original letter, pointing out and apologising for the oversight.'

Colonis submitted that it did not mention any further details relating to the corrective mailing in responding to Case AUTH/3240/8/19 as it had fully disclosed this in its response to Case AUTH/3239/8/19 on the same day. It would appear that Colonis inadvertently assumed both cases would be considered together as they both related to the same item, were dated the same day and the responses were submitted on the same day; and Colonis noted that the PMCPA wrote to it advising of the outcomes of all three cases on 12 December 2019.

Colonis apologised for any confusion this might have caused and there was certainly no intention whatsoever to be anything other than completely open and transparent with the Panel in its responses. In Colonis' view, the imposition of additional sanctions under Paragraph 11.1 of the Constitution and Procedure would not be appropriate for the following reasons:

1 At most, as explained above, the omission of 'required and agreed by the MHRA' in referring to the 'corrective mailing' in our response to Case AUTH/3240/6/19 was an inadvertent oversight.

2 The case report for Case AUTH/3240/8/19 which would be published on the PMCPA website would state as follows:

> > 'During the consideration of this case, the Panel noted Colonis' submission that the company sent a corrective letter on 23 July to the recipients of the original letter to point out and apologise for the oversight in relation to the incorrect prescribing information. Colonis' submission made no reference to the MHRA in this regard. However, the Panel noted that Colonis' submission to Case AUTH/3239/8/19 stated that the company had received a letter from the MHRA stating that they had been in receipt of several complaints in relation to off-label promotion and following correspondence with the MHRA "we sent an agreed corrective mailing". The corrective mailing, dated 24 July, stated "The MHRA have asked Colonis Pharma to provide a corrective statement …". The Panel noted that this corrective statement referred to a number of issues with the original promotional letter including the provision of incorrect prescribing information. The Panel queried why Colonis in Case AUTH/3240/8/19 did not refer to the company's correspondence with the MHRA in this regard. Self-regulation relied on complete and accurate responses from companies.'

3 Colonis had already been found to have been in breach of Clause 2 of the Code which was a sign of particular censure.

APPEAL BOARD CONSIDERATION

The Appeal Board noted the Panel's rulings of breaches of Clauses 2, 4.1 and 9.1 of the Code. The Appeal Board noted that the company had apologised and admitted that it had made errors. The company submitted that these were administrative errors due to its unfamiliarity with the complaints procedure and a lack of understanding of the importance or relevance of the information which should have been provided. The Appeal Board noted that Colonis had failed to state in its response to Case AUTH/3240/8/19 that the corrective letter on 23 July was required by the MHRA. Although the response to Case AUTH/3239/8/19 included a copy of the corrective statement in question the company's letter should have been clearer that the MHRA required a corrective statement to be sent. The information included in Case AUTH/3239/8/19 was clearly relevant to the current case, Case AUTH/3240/8/19. Both responses had been sent to the Authority by Colonis on the same day. The Appeal Board noted that any case under the Code must stand alone and be considered on its individual merits. Case AUTH/3239/8/19 and Case AUTH/3240/8/19 had not been amalgamated under Paragraph 5.1 of the Constitution and Procedure. It was essential that companies had an in depth understanding of the Code and the Constitution and Procedure including responding to complaints. The Appeal Board noted that self-regulation relied, *inter alia*, upon the provision of complete and accurate information from pharmaceutical companies.

The Appeal Board noted Colonis' submission that it was a subsidiary of Clinigen set up to develop and bring to market products that were currently used as specials. The Appeal Board noted the area in which Colonis was working in and the apparent lack of Code knowledge which was of concern. The Appeal Board noted, however, that the company was in the process of being fully integrated into Clinigen which should bring increased compliance resource and oversight.

The Appeal Board decided that, in accordance with Paragraph 11.3 of the Constitution and Procedure, Colonis should be publicly reprimanded for its failure to provide complete and accurate information to the Panel.

The Appeal Board gave consideration to the use of further sanctions but decided that, on balance, none were required.

Voluntary Admission received **15 August 2019**

Undertaking received **20 December 2019**

Appeal Board consideration **22 January and 26 February 2020**