CASE AUTH/3611/2/22

COMPLAINANT v DAIICHI SANKYO

Electronic guidelines card for Nilemdo and Nustendi

CASE SUMMARY

This case was in relation to a NICE technology appraisal summary card for Nilemdo (bempedoic acid) and Nustendi (bempedoic acid and ezetimibe), produced as promotional material by Daiichi Sankyo, which allegedly did not mention the contraindication with simvastatin >40mg nor the importance of seeing Sections 4.2, 4.3, and 4.4 of the Summary of Product Characteristics (SPC).

The Panel ruled a breach of the following Clause(s) of the 2021 Code for failing to make immediately apparent to health professionals in promotional material which referred to the therapeutic use of Nilemdo or Nustendi in combination with a statin that there was a contraindication regarding concomitant use with simvastatin >40mg daily:

Breach of Clause 6.1	**Misleading impression provided**
Breach of Clause 6.2	**Misleading impression incapable of substantiation**
Breach of Clause 5.1	**Failure to maintain high standards**
Breach of Clause 2	**Bringing discredit upon, and reducing confidence in, the pharmaceutical industry**

The Panel ruled no breach of the following Clause(s) of the 2021 Code based on the complainant not having established, on the very narrow allegation, that there was 'no mention at all anywhere on the card about the contraindication with simvastatin >40mg', nor that by not instructing the reader to view Sections 4.2, 4.3 and 4.4 of the SPC meant that Nilemdo and Nustendi had been promoted outside the terms of their licences as alleged:

No Breach of Clause 6.1	**The requirement to not mislead either directly or by implication, by distortion, exaggeration or undue emphasis**
No Breach of Clause 11.2	**The requirement for promotion to not be inconsistent with the SPC**

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

FULL CASE REPORT

A complainant who described him/herself as a health professional had concerns about an electronic guidelines card for Nilemdo (bempedoic acid) and Nustendi (bempedoic acid and ezetimibe). The material (dated May 2021, BEM/21/0086), commissioned and funded by

Daiichi-Sankyo, was hosted on guidelines in practice and was headed 'NICE Technology appraisal 694'.

COMPLAINT

The complainant stated that both Nilemdo and Nustendi were contra-indicated with concomitant use with simvastatin >40 mg daily. The complainant stated that in the summary of product characteristics (SPC), the licensed indications section for both medicines gave clear guidance to see Sections 4.2, 4.3, and 4.4 around use with simvastatin. The complainant alleged that there was no mention at all anywhere on the guidelines card about the contra-indication with simvastatin >40mg. The marketing authorisation indications that were referred to on the card did not mention about the importance of seeing Sections 4.2, 4.3, and 4.4 which was allegedly promoting outside of the SPC. Without this key information, it was misleading to the audience as the card was easily interpreted that any dose of simvastatin was suitable to use with Nilmedo and Nustendi.

When writing to Daiichi-Sankyo, the Authority asked it to consider the requirements of Clauses 2, 5.1, 6.1, 6.2 and 11.2 of the Code as cited by the complainant.

RESPONSE

Daiichi Sankyo submitted that it took its obligations under the Code seriously and strove to maintain high standards and behaved responsibly and ethically at all times.

Daiichi Sankyo denied all the alleged breaches.

Daiichi Sankyo confirmed that the electronic guidelines card referred to by the complainant was a NICE TAG summary card entitled 'NICE Technology Appraisal 694: Bempedoic acid▼ with ezetimibe for treating primary hypercholesterolemia or mixed dyslipidaemia' (Job code: BEM/21/0086, Date of preparation: May 2021) and it was launched on 4 June 2021.

The summary card was available for general practitioners, payors and policy makers who were registered to the Guidelines website: https://www.guidelines.co.uk/ which was intended for UK health professionals. The NICE TAG summary card was scheduled for 6 months availability on the website, and it was removed on 3 December 2021. It was reapproved for electronic use for the Daiichi Sankyo UK representatives to be used with health professionals. The intention of the material was to provide a summary of the guidance as outlined by NICE TA694 on the use of bempedoic acid with ezetimibe for treating primary hypercholesterolemia or mixed dyslipidaemia. The information provided in the summary card was cited directly from the recommendations outlined in the relevant sections within NICE TA694 (copy provided). It did not include any further information, claims or comparisons that would require extra substantiation other than what was provided on the piece.

Allegation 1 - '*there was no mention at all anywhere on the card about the contra-indication with Simvastatin >40mg*'.

Daiichi Sankyo submitted that the promotional item contained the prescribing information in line with the requirements of the Code. There was clear sign posting of where the prescribing information could be found.

The prescribing information on pages 3 and 4 of the summary card provided the required information in line with the requirements of the Code, including '**Contraindications**' for use of both Nilemdo and Nustendi, respectively. Under the heading '**Contraindications**' for both products, the statement 'concomitant use with simvastatin >40mg daily' could be found.

The '**Contraindications**' heading, as well as all relevant information headings in the prescribing information, were emphasised prominently in bold font, so that the audience could easily locate this information. In addition, there was a clear statement at the top of the prescribing information directing the reader to '*Refer to the Summary of product of characteristics (SmPC) prior to prescribing'*. Daiichi Sankyo therefore disagreed with the complainant's allegation that *'there was no mention at all anywhere on the card about the contra-indication with Simvastatin >40mg*'.

Allegation 2 - '*The marketing authorisation indications that were referred to on the card did not mention about the importance of seeing sections 4.2, 4.3, and 4.4 which was promoting outside of the SPC. Without this key information, it was misleading to the audience'.*

Daiichi Sankyo submitted that the information in '*sections 4.2, 4.3, and 4.4*' to which the complainant referred, was referencing where readers of the SPC could find additional information available within the SPC for both Nilemdo and Nustendi. The SPC for Nilemdo and Nustendi included sections listed as: 4.1 Therapeutic indications, 4.2 Posology and method of administration, 4.3 Contraindications and Section 4.4 Special warnings and precautions for use. It was not a Code requirement to include the entire SPC sections within promotional materials, instead Daiichi Sankyo was required to include the pertinent sections as a summary in the prescribing information. The information that was contained within Sections 4.2, 4.3 and 4.4 of the SPC had been provided as part of the prescribing information for both Nilemdo and Nustendi which could be found on pages 3 and 4 of this NICE TAG Summary Card. The indications and information outlined in the prescribing information provided within the material, within the body of the NICE TAG summary card and NICE TA694, were all in line and consistent with the SPC for both products. Daiichi-Sankyo UK therefore completely disagreed with the complainant's allegation that this was '*promoting outside of the SPC'.*

Daiichi Sankyo submitted that clear instructions on the location of the prescribing information were also provided with a clear and prominent statement on the bottom of pages 1 and 2 of the NICE TAG summary card directing readers to the prescribing information on page 3 and 4. Therefore, Daiichi Sankyo disagreed with the complainant's allegation suggesting that key information was not provided and as a consequence, this was not misleading to the audience and could be substantiated as described above.

In recognition of the importance of a reader easily accessing and referring to the SPC for further information, Daiichi Sankyo wanted to highlight that it had taken measures to include this information as part of the NICE TAG summary card. In NICE TA694, under Sections 2.3 and 2.4, there was a clear section referring readers to access the dosage schedule in the marketing authorisation.

Daiichi Sankyo pointed out that it had provided the SPC as hyperlinks for readers to access, reflective of the information provided in the 'Dosage in the marketing authorisation' section of the NICE recommendations.

Furthermore, in recognition that this was a 'summary card' there was a clear, prominent box highlighted in orange, underneath the NICE TA694 guidance advising the audience to refer to the full appraisal: '*This summary card only displays the concise technology appraisal; readers are strongly advised to refer to the full appraisal at www.nice.org.uk/guidance/ta694'.*

Daiichi Sankyo UK further refuted the complainant's allegation that '*It was concerning that the medical lead for Nilemdo and Nustendi had allowed this card to be published without the key information around not using with Simvastatin >40mg*'. As outlined above the prescribing information provided as part of this promotional material contained information on all contraindications listed for both Nilemdo and Nustendi which included a clear statement on concomitant use with Simvastatin >40mg daily.

Daiichi Sankyo refuted the allegation that this item breached Clauses 6.1 or 6.2. The item was balanced, fair, objective, unambiguous and based on the most up-to-date guidance from the NICE Technology appraisal on Daiichi-Sankyo's products. The item had sufficient information to enable the reader to form their own opinion of the therapeutic value of the medicines. The information on the NICE TAG summary card had been cited directly from the NICE guidelines, which were readily accessible and did not include any claims or comparisons which might require additional information for substantiation.

Daiichi Sankyo submitted that the NICE TAG summary card had been reviewed and certified to ensure consistency with both the Nilemdo and Nustendi licence. There was no evidence that Daiichi Sankyo had promoted inconsistently with the particulars listed in the SPC, and it therefore disagreed with the alleged breach of Clause 11.2. Consequently, as there had been no breach of Clauses 6.1, 6.2 and 11.2, there was no evidence that high standards had not been maintained (Daiichi Sankyo denied a breach of Clause 5.1). Overall, there was no evidence that Daiichi Sankyo had prejudiced patient safety and Daiichi Sankyo denied a breach of Clause 2.

Daiichi Sankyo submitted that it had acted in line with the requirements of the Code, maintained high standards, and had not brought discredit upon, or reduced confidence in, the industry.

PANEL RULING

The Panel noted that the material at issue was a NICE TAG summary card entitled 'NICE Technology Appraisal 694: Bempedoic acid▼ with ezetimibe for treating primary hypercholesterolemia or mixed dyslipidaemia'. The Panel noted that the material at issue consisted of four pages and had been commissioned and funded by Daiichi Sankyo UK. The first two pages referred to the NICE technology appraisal and the last two pages contained prescribing information for Nilemdo and Nustendi, respectively.

The Panel noted that beneath the subheading 'Bempedoic acid (Nilemdo®▼) & Bempedoic acid and ezetimibe (Nustendi®▼): NICE TA694' were two distinctly set out sections. Section 1 of the material, headed Recommendations, was on page 1 and was referenced to NICE technology appraisal guidance (TA694). Section 2, also referenced to NICE technology appraisal guidance (TA694), was displayed parallel to Section 1, continuing on to page 2, and gave information about bempedoic acid and bempedoic acid-ezetimibe, including their licensed indications, which were broader than the NICE recommendation.

In relation to the complainant's allegation that there was no mention anywhere on the card of the contraindication with simvastatin >40mg, the Panel noted Daiichi Sankyo's submission that the material contained prescribing information on pages 3 and 4 and reference to where the prescribing information could be found was at the bottom of pages 1 and 2, in bold font. The Panel further noted Daiichi Sankyo's submission that the prescribing information contained headings, including for 'contraindications', which were emphasised prominently in bold font so that the audience could easily locate this information and there was a statement at the top of the prescribing information directing the reader to 'Refer to the Summary of product of characteristics (SmPC) prior to prescribing'.

The Panel noted that both the Nilemdo and Nustendi SPCs, under Section 4.3 Contraindications, listed, *inter alia*, 'concomitant use with simvastatin >40mg daily'. The prescribing information for both Nilemdo and Nustendi on the guidelines summary card at issue also listed 'concomitant use with simvastatin >40mg daily' under 'Contraindications'.

The Panel considered, based on the very narrow allegation, that the complainant had not established that there was 'no mention at all **anywhere on the card** about the contraindication with simvastatin >40mg' (emphasis added by the Panel), as alleged, and no breach of Clause 6.1 was ruled in that regard.

The Panel noted that the complainant alleged that in not mentioning the importance of reading Sections 4.2, 4.3 and 4.4 of the SPC, this was promoting Nilmedo and Nustendi outside of their respective SPCs, and that without this key information, it was misleading to the audience as the material at issue implied that any dose of simvastatin was suitable to use with Nilemdo and Nustendi.

The Panel noted that Section 4.1, Therapeutic indications, of the Nilemdo and Nustendi SPCs each referred the reader to Sections 4.2 (posology and method of administration), 4.3 (contraindications) and 4.4 (special warnings and precautions for use) when referring to the use of each medicine in combination with a statin (emphasis added by the Panel below):

> 'Nilemdo is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:
> o **in combination with a statin** or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin **(see sections 4.2, 4.3, and 4.4)** or,
> o alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.'
>
> 'Nustendi is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:
> o **in combination with a statin** in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin in addition to ezetimibe **(see sections 4.2, 4.3, and 4.4),**
> o alone in patients who are either statin-intolerant or for whom a statin is contraindicated, and are unable to reach LDL-C goals with ezetimibe alone,
> o in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin.'

The Panel considered that Sections 4.2, 4.3 and 4.4 of the SPC gave important safety information in relation to concomitant use with simvastatin including that both Nilemdo and Nustendi were contraindicated in patients taking simvastatin >40mg daily.

The Panel considered that whether a contraindication needed to be highlighted within a particular section of promotional material, in addition to its requirement to be included within the prescribing information that was required on all promotional material, depended on a consideration of all of the circumstances including the nature of the contraindication and the content, layout, audience and intended use of the material.

The Panel noted that the material at issue was commissioned and funded by Daiichi Sankyo and was promotional material; it thus needed to comply with the requirements of the Code including that the material must be sufficiently complete to enable recipients to form their own opinion of the therapeutic value of the medicine and must not be misleading. It was an established principle that companies could not rely on prescribing information to qualify a claim or negate a misleading impression.

The Panel noted the intention of the material at issue was to provide a summary of NICE guidance. However, whilst the Panel noted Section 1 referred to the NICE recommendation which was to use only if statins are contraindicated or not tolerated, the Panel noted that the indications for Nilemdo and Nustendi in Section 2 were presented parallel to Section 1 and were included with the same prominence, and were far broader than the NICE recommendation and specifically referred to therapeutic use in combination with a statin.

The Panel considered the immediate and overall impression of the material to a busy health professional. In the Panel's view, given that simvastatin was a commonly prescribed lipid lowering treatment, the contraindication regarding concomitant use with simvastatin >40mg daily needed to be immediately apparent to health professionals in promotional material which referred to therapeutic use of Nilemdo or Nustendi in combination with a statin. The Panel, noting that the body of the material specifically made reference to therapeutic use of Nilemdo and Nustendi in combination with a statin, considered that the material should have made the contraindication in patients taking simvastatin >40mg daily immediately apparent to readers. The Panel considered that the sole inclusion of this contraindication in the prescribing information was not sufficient in this regard and did not negate the misleading immediate impression given that Nilemdo and Nustendi could be used in combination with any dose of any statin which was not so. Therefore, a breach of Clause 6.1 was ruled. The misleading impression was not capable of substantiation and a breach of Clause 6.2 was ruled.

Whilst the Panel considered the importance of highlighting the contraindication with simvastatin>40mg in the body of the material as per its comments and rulings above, the Panel did not consider that the complainant had established that by not instructing the reader to view Sections 4.2, 4.3 and 4.4 of the SPC, which made reference to the contraindication, meant that Nilemdo and Nustendi had been promoted outside the terms of their licences as alleged. No breach of Clause 11.2 was ruled in that regard.

The Panel noted its comments and rulings above and considered that Daiichi-Sankyo had failed to maintain high standards and a breach of Clause 5.1 was ruled.

The supplementary information to Clause 2 listed prejudicing patient safety as an activity likely to lead to a breach of that clause. The Panel was concerned that in referring to therapeutic use

in combination with a statin on page 1 of the material, without mentioning that Nilemdo and Nustendi were contraindicated with simvastatin>40mg daily until page 3, where it appeared within the prescribing information in small text, particularly given that simvastatin was a commonly prescribed statin, meant that there was a risk that some patients on simvastatin >40mg daily might be inappropriately treated with Nilemdo or Nustendi. Patient safety was of the utmost importance and the Panel considered that the contraindication with simvastatin >40mg daily was not immediately apparent when reference to therapeutic use with a statin was referred to which might prejudice patient safety and was such as to reduce confidence in, and bring discredit upon, the pharmaceutical industry. A breach of Clause 2 was ruled.

Complaint received **14 February 2022**

Case completed **23 February 2023**