CASE AUTH/3677/7/22

COMPLAINANT v DAIICHI SANKYO

Promotion of Nilemdo and Nustendi

CASE SUMMARY

This case was in relation to allegations that representatives promoting Nilemdo and Nustendi did not make clear within sales calls using sales aids and leavepieces that these products should not be used in combination with a simvastatin dosage greater than 40mg. The complainant was further concerned that representatives had not been trained properly or given clear briefing in this regard.

The Panel ruled a breach of the following Clauses of the 2021 Code because in its view:

- **certain slides within the two sales aids (refs BEM/21/0626 and BEM/21/0828) specifically made reference to the therapeutic use of Nilemdo and Nustendi in combination with a statin but those slides did not make the contraindication in patients taking simvastatin >40mg daily immediately apparent to readers. The inclusion on subsequent slides was not sufficient to negate the misleading impression given that Nilemdo and Nustendi could be used in combination with any dose of any statin, which could not be substantiated.**

- **the failure to refer to the contraindication with simvastatin > 40mg on the first and fourth pages of two leavepieces (ref BEM/21/0653 and BEM/21/0816) gave the misleading impression that Nilemdo and Nustendi could be used in combination with any dose of simvastatin which was not so and reference to the contraindication on the other pages was not sufficient to negate the misleading impression which could not be substantiated.**

- **within the two briefing documents (BEM/21/0827 and BEM/21/0829), it was not made sufficiently clear that Nilemdo and Nustendi could not be used in combination with simvastatin > 40mg, whenever there was reference to combination with statins or other lipid-lowering therapies (LLTs), and therefore representatives had not been given clear briefing on the contraindications with simvastatin and the need to mention it when making claims about combining Nilemdo and Nustendi with other cholesterol lowering agents as alleged.**

- **a number of concerns had been raised across a number of materials and breaches of the Code had been ruled and it considered that the repeated failure to comply with the Code on this matter was particularly serious and might prejudice patient safety and was such as to reduce confidence in, and bring discredit upon, the pharmaceutical industry.**

Breach of Clause 6.1	**Making a misleading claim**

Breach of Clause 6.2	**Making an unsubstantiated claim**
Breach of Clause 5.1	**Failing 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 Clauses of the 2021 Code because:

- **it noted that the complainant's allegation related to general training activities rather than the specific briefing materials considered and ruled in breach of the Code above, and considered, based on the evidence before it, that it had not been established that representatives had not been trained properly on mandatory contraindications around simvastatin as alleged**

- **on balance, noting that the complainant had not detailed specific sales calls, it considered on this very narrow ground that it had not been established that representatives did not make clear reference to the contraindication with simvastatin >40mg during sales calls as alleged:**

No Breach of Clause 6.1	**Requirement that claims/information/comparisons must not be misleading**
No Breach of Clause 17.1	**Requirement that representatives must be given adequate training and have sufficient scientific knowledge to enable them to provide full and accurate information about the medicines which they promote**

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 who described themselves as a health professional about the promotion of Nilemdo (bempedoic acid) and Nustendi (bempedoic acid and ezetimibe).

COMPLAINT

The complainant alleged that sales representatives promoting Nilemdo and Nustendi did not make clear that these products should not be used in combination with a simvastatin dosage greater than 40mg. The representatives utilised a sales aid on the products and hard copy promotional leavepieces which discussed combining Nilemdo and Nustendi with other cholesterol-lowering medications.

The complainant stated that it was troubling that representatives did not make clear reference to simvastatin within sales calls using the sales aids and leavepieces, considering this was a gold standard of care in high cholesterol management and was mentioned in the regulatory document of Nilemdo and Nustendi. The promotional sales aid and hard copy promotional leavepieces were used during April 2021-February 2022. The complainant alleged that although both materials made claims about combining Nilemdo and Nustendi by adding to other

medications, it was not made obvious to prescribers that there was a contraindication by adding to simvastatin >40mg within the materials themselves. The complainant was concerned that representatives had not been trained properly or given clear briefing within the materials on mandatory contraindications around simvastatin and the need to mention these at all times when making claims about combining Nilemdo and Nustendi with other cholesterol-lowering agents. The complainant alleged breaches of Clauses 17.1, 17.9, 5.1, 6.1, 6.2 and 2 had been breached as an act of using the sales aid and hard copy promotional pieces within calls.

When writing to Daiichi Sankyo, the Authority asked it to consider the requirements of Clauses 2, 5.1, 6.1, 6.2, 17.1 and 17.9 of the 2021 Code.

RESPONSE

Daiichi Sankyo stated that it took its obligations under the Code of Practice seriously, and it strove to maintain high standards and always behaved responsibly and ethically.

Daiichi Sankyo submitted that the complaint did not contain specific information as to which sales aids or which hard copy promotional leavepieces or which calls 'that representatives did not make clear reference to Simvastatin within sales calls using the sales aids and leavepieces'. Owing to the lack of evidence provided, Daiichi Sankyo was therefore unable to provide a more precise response to these broad and speculative allegations.

As the complainant had not provided any evidence to substantiate any of the allegations, Daiichi Sankyo presented below the measures that were in place to ensure that its sales representatives:

- Received the training required to communicate safety information, including training on the SPC for Nilemdo and Nustendi

AND

- Demonstrated that they had access to appropriate materials and resources to communicate important safety information on all Daiichi Sankyo UK products during their interactions with health professionals which included communicating the contraindication listed in the SPC for both Nilemdo and Nustendi on concomitant use with simvastatin >40mg.

Daiichi Sankyo outlined the measures that had been put in place by the company since the outcome of [Case AUTH/3504/4/21] where Daiichi Sankyo was found in breach for having the simvastatin contraindication mentioned as part of a footnote. Daiichi Sankyo addressed these issues in sequential order below.

Daiichi Sankyo stated that its sales representatives went through an extensive Initial Training Course (ITC) upon joining the company, which contained specified training allocations on the individual product summaries of product characteristics (SPCs). In this case, training on both Nilemdo and Nustendi. The Standard Operating Procedure (SOP) on representatives' standards could be found as part of the enclosures which documented the training requirements for the representatives.

In addition, Daiichi Sankyo provided a screenshot of the section of the SPC validation test that specifically focused on the concomitant use with simvastatin >40mg warning for use with Nilemdo. The full SPC validation quiz was provided as part of the enclosures.

With respect to the 'sales aid' referred to by the complainant, Daiichi Sankyo confirmed that all sales aids that had been developed and approved for electronic use by representatives (inclusive of the time period to which the complainant referred, April 2021-February 2022) in their discussions to support the promotion of Nilemdo and Nustendi; contained dedicated sections on each of the products' safety information, including information on all contraindications and special warnings and precautions.

Daiichi Sankyo provided screenshots of the sections of the sales aids (refs BEM/21/0462, BEM/21/0826 and BEM/21/0828) that clearly highlighted the contraindication of concomitant use with simvastatin >40mg.

Daiichi Sankyo submitted that to accompany this material, the briefing documents developed for use with these sales aids contained briefing information on the included safety slides. Daiichi Sankyo provided screenshots of the briefing documents (refs BEM/21/0461, BEM/21/0829 and BEM/21/0827) to demonstrate that the objective of the slides was to ensure that information regarding concomitant medicines contraindications and special warnings was addressed, which included the warnings on concomitant simvastatin use under the 'KEY TAKEAWAYS' for physicians.

Daiichi Sankyo submitted that as per the information provided, including the supporting documentation as part of the enclosures, contrary to the complainant's allegation, Daiichi Sankyo refuted the complainant's allegation 'that representatives had not been trained properly or given clear briefing within the materials on mandatory contra-indications around simvastatin and the need to mention these at all times when making claims about combining Nilemdo and Nustendi with other cholesterol lowering agents'.

In line with the requirements of Clause 17.1, Daiichi Sankyo submitted that it could demonstrate that representatives had been trained on the SPC for both products which was inclusive of all safety warnings and contraindications and had been briefed appropriately on communicating the safety information related to Nilemdo and Nustendi, which included the contraindications around simvastatin. There was no breach of Clause 17.1.

Additionally, in line with the requirements of Clause 17.9, and as demonstrated above, Daiichi Sankyo confirmed that representatives had been provided with training materials on the medicines in question along with instructions as to how the product should be promoted. The briefing materials provided facilitated representatives to have sufficient scientific knowledge, enabling them to provide full and accurate information about the medicines which they promoted. Therefore, Daiichi Sankyo believed that the briefing material accompanying these materials (as shown above) complied with the relevant requirements of the Code and had been certified under the requirements of Clause 8, therefore there was no breach of Clause 17.9.

Daiichi Sankyo submitted that as the safety information provided in the sales aid on all the contraindications and safety precautions to be considered for both Nilemdo and Nustendi, was fair, balanced, accurate, objective and unambiguous, did not mislead and enabled recipients to form their own opinion of the therapeutic value of the medicine, there was no breach of Clause

6.1. As the information presented could also be substantiated in the SPC for both Nilemdo and Nustendi, there was therefore no breach of Clause 6.2.

Daiichi Sankyo submitted that as part of [Case AUTH/3504/4/21], it signed an undertaking in December 2021 for having the simvastatin contraindication mentioned as part of a footnote. As a result of [Case AUTH/3504/4/21], Daiichi Sankyo had implemented the following steps and processes below:

- Immediately withdrew the website that was the subject of the original complaint.
- Conducted a full review of Nilemdo and Nustendi promotional materials to ensure other materials potentially affected were identified.
- Conducted a recall of all materials impacted and replaced them with revised content making the simvastatin contraindication disclaimer clear where required.
- Briefed relevant Daiichi Sankyo staff on the case findings, implications and learnings.
- Updated all internal documents to reflect the changes and requirements for promotional materials as a result of the case findings.

Daiichi Sankyo stated, as a result of this, no promotional sales aid or hard copy leavepieces were used consistently from April 2021 through to February 2022 which was contrary to the complainant's broad and inaccurate allegation above.

Daiichi Sankyo submitted that all affected promotional materials, which included electronic sales aids and hard copy leavepieces, were recalled and updated in line with the undertakings from the breach, and the simvastatin warning was added to all relevant sections which contained claims which had been subject to the original complaint outlined in Case [AUTH/3504/4/21]. As communicated above, the safety sections with information on the contraindications/special warnings and precautions had been consistently present, since approved in July 2020, in all sales aids which were developed as part of the promotional campaign. The content of these sections within the sales aids had been unaffected since the case findings and had always been accessible for representatives to use in their interactions with health professionals for which they had been briefed and trained accordingly.

Daiichi Sankyo stated that it therefore refuted the allegation that 'Although both materials made claims about combining Nilemdo and Nustendi by adding to other medications, it was not made obvious to prescribers that there was a contra-indication by adding to simvastatin >40mg within the materials themselves'.

<u>Additional comments from Daiichi Sankyo:</u>

Daiichi Sankyo submitted that as the Panel would be aware, Daiichi Sankyo has recently been subject to a number of complaints of a similar theme, submitted by an anonymous complainant. The repetitive theme of the allegations contained within these complaints appeared to have arisen following the outcome of [Case AUTH/3504/4/21] where Daiichi Sankyo was found in breach for having the simvastatin contraindication mentioned as part of a footnote. As outlined above, and as a result of Case [AUTH/3504/4/21], Daiichi Sankyo implemented a number of actions and processes below to rectify any affected materials following this breach, however, it appeared that the complainant was essentially searching for any materials/activities that Daiichi Sankyo would have produced in the time period prior to having been found in breach for this case, inferring that this warning should be on every Daiichi Sankyo material, irrespective of the content, context and intent of these materials.

Within the complaints submitted, the PMCPA would likely also have noticed the somewhat malicious and defamatory nature of the wording directed towards the medical signatory team. If they were the complainant, they had clearly misled the Panel in the course of their complaints in their identity. More concerningly, there had been no attempt to achieve resolution through inter-company dialogue, and at no point had the complaint been voiced directly to Daiichi Sankyo. It was disappointing that some individuals chose to use complaints to the PMCPA as a method of communicating their concerns which contradicted the spirit of the Code and Daiichi Sankyo's responsibilities and autonomy as an industry to self-regulate.

Daiichi Sankyo stated that, through its Ethics and Compliance Committee, it had implemented a 'Speak Up' facility within the organisation and had communicated throughout the business on its 'Speak Up' culture, seeking to create a psychologically-safe culture where Daiichi Sankyo staff could speak up and share any concerns. There was also an option of doing so anonymously. Daiichi Sankyo asked that the Panel took all of this into consideration from a broader perspective regarding consideration of anonymous complaints.

Summary

Based on the response provided above and material submitted, Daiichi Sankyo refuted all allegations of Code breaches. As there had been no breach of Clauses 17.1, 17.9, 6.1 or 6.2, there was no evidence that high standards had not been maintained meaning that there had not been a breach of Clause 5.1. Consequently, there was no evidence to suggest that Daiichi Sankyo had prejudiced patient safety and thus no breach of Clause 2. Daiichi Sankyo took its obligations under the Code seriously, and strove to maintain high standards and always behave responsibly and ethically.

PANEL RULING

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:
>
> - 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,
> - 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:
>
> - 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**).

- 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,
- in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin.'

The Panel noted that Sections 4.2, 4.3 and 4.4 of the Nilemdo and Nustendi SPCs 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. It was an established principle that companies could not rely on footnotes or prescribing information to negate a misleading impression.

The Panel noted Daiichi Sankyo's submission that as part of [Case AUTH/3504/4/21], it had signed an undertaking in December 2021 for having the simvastatin contraindication mentioned as part of a footnote and, as a result, had implemented certain steps to identify, withdraw and recall certain materials and replace them with revised content making the simvastatin contraindication clear where required, brief relevant staff and update internal documents to reflect the changes as a result of the case findings.

The Panel noted Daiichi Sankyo's submission that the simvastatin warning was added to all relevant sections which contained claims which had been subject to the original complaint outlined in [Case AUTH/3504/4/21].

The Panel noted the complainant's allegation that Daiichi Sankyo had failed to ensure sales representative activities, training, briefing materials and materials used made clear the contraindication with simvastatin >40mg when discussing the combination of Nilemdo and/or Nustendi with other cholesterol-lowering medications. In this regard, the complainant did not provide any specific details regarding representative's activities but referred to a promotional sales aid and hard copy leavepieces used by representatives between April 2021-February 2022. The Panel noted Daiichi Sankyo's submission that no promotional sales aid or hard copy leavepieces were used consistently from April 2021 through to February 2022 but noted that the complainant was, nonetheless, clear about the time period which was the subject of their concern. The Panel therefore based its rulings on the materials provided by Daiichi Sankyo as part of its enclosures, bearing in mind the relevant time period.

Whilst Daiichi Sankyo provided three electronic sales aids as part of its enclosures, (refs BEM/21/0462, June 2020, BEM/21/0826, December 2021 and BEM/21/0828, December 2021), it appeared only the latter two, a short and long sales aid respectively, were current during the relevant time period, April 2021-February 2022. The Panel therefore based its rulings on these two sales aids and the briefing documents associated with them (refs BEM/21/0827; December 2021 and BEM/21/0829; February 2022) and the two leavepieces provided by Daiichi Sankyo (refs BEM/21/0653, January 2022 and BEM/21/0816, December 2021)

Sales aids (refs BEM/21/0626 and BEM/21/0828)

The Panel noted the short sales aid (ref BEM/21/0626, December 2021) contained a number of menu buttons at the bottom including icons that linked to prescribing information, references and abbreviations and a hamburger icon. The hamburger icon, when expanded, appeared to display the various sections of the sales aid as follows: 'Impact of high LDL-C', 'Nilemdo® And Nustendi®', 'Mechanism of action', 'Efficacy', 'Tolerability' and 'Summary'.

The Panel noted the long sales aid (ref BEM/21/0828, December 2021), was similar in this regard but included a hamburger icon which when expanded, appeared to display 'Clinical Challenges', 'Impact of high LDL-C', 'Guidelines', 'Nilemdo® And Nustendi®', 'Mechanism of action', 'Efficacy', 'Tolerability', 'Dosing and 'Summary'.

The Panel noted the opening slide (1/86) of the long sales aid (ref BEM/21/0828), was almost identical to slide 3/47 of the short sales aid, (ref BEM/21/0826). Each slide contained the logos of Nilemdo and Nustendi in the top right-hand corner with the strapline 'Add on to take back control', with an image of a woman and her doctor pulling what appeared to be cholesterol into a hole accompanied by the statement 'IN THE STRUGGLE AGAINST ELEVATED LDL-C, ADD ON TO BRING DOWN'. Below the image it stated 'Discover how you and your patients can lower LDL-C' below which, following an instruction to consult the relevant SmPC prior to prescribing, were the indications for Nilemdo and Nustendi in smaller font:

> 'NILEMDO® is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet: in combination with a statin or statin with other lipid-lowering therapies (LLTs) in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin; or alone or in combination with other LLTs 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: 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; 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; or in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin.'

The Panel, noting its reproduction of the complete Nilemdo and Nustendi SPC indications at the beginning of the ruling above, noted that the reference to the information in Sections 4.2, 4.3 and 4.4 of the SPCs, in relation to concomitant use with statins, was omitted from the indication on this slide in both detail aids.

The Panel noted that slide 7/47 of the short sales aid (ref BEM/21/0826) and slide 18/86 of the long sales aid (ref BEM/21/0828) were similar and appeared to sit within the 'Nilemdo® and Nustendi®' section of each, and were titled 'ADD ON NILEMDO OR NUSTENDI TO TAKE BACK CONTROL', the slide then had a box which included the Nilemdo and Nustendi logos stating below:

> 'are oral options that contain bempedoic acid which has a novel mechanism of action. They can be added to existing oral LLTs to help deliver the additional LDL-C reductions that uncontrolled patients need. Concomitant use with simvastatin > 40 mg is contraindicated; please refer to the SmPC for use with statins.'

An icon labelled 'INDICATION' appeared to the right of this box which appeared to be a link to the Nustendi and Nilemdo indications and the slide that followed (Slide 8/47 of the short sales aid and slide 20/86 of the long sales aid) gave the indication of each medicine. On this indication slide in each sales aid, there was, again, no reference to the information in relation to concomitant use with statins within Section 4.2, 4.3 and 4.4 of the SPCs.

The Panel noted that Slide 8/86 of the long sales aid was titled 'CVD IS RESPONSIBLE FOR 1 IN 4 DEATHS IN ENGLAND, EQUATING TO 1 DEATH EVERY 4 MINUTES' and stated 'Around 80% of hypercholestrolaemia patients on moderate- or high-intensity statins remain uncontrolled and at increased CV risk' followed by 'Additional LLTs are needed to complement current therapies to help uncontrolled patients achieve their LDL-C goals'. There was, however, no reference to the contraindication with simvastatin > 40 mg on this slide. The Panel noted that slide 13/86 of the long sales aid (ref BEM/21/0828) titled 'The ESC/EAS GUIDELINES RECOMMEND INTENSIVE REDUCTION OF LDL-C IN UNCONTROLLED PATIENTS TO REDUCE CV RISK' included the statement 'The ESC/EAS Guidelines recommend adding a non-statin LLT to a maximally tolerated statin therapy' which, in the Panel's view, within a promotional sales aid for Nilemdo and Nustendi promoted the addition of these two medicines to maximally tolerated statin therapy but no reference was made to the contraindication with simvastatin > 40 mg.

The Panel further noted that the long sales aid referred to clinical studies from slide 28/86 including 'CLEAR Harmony', 'CLEAR Wisdom' and 'Study 053' which referred to Nilemdo in the first two and Nustendi in the latter being added to a maximally tolerated statin. The results of the 'CLEAR Harmony', 'CLEAR Wisdom' and '053' studies were set out on separate slides (30/86, 34/86, and 46/86 respectively) each titled 'NILEMDO AND NUSTENDI DELIVERED SIGNIFICANT LDL-C REDUCTIONS ON TOP OF CURREMT ORAL LLTS'. The Panel noted that the contraindication with simvastatin > 40mg was not mentioned on any of these slides.

The Panel noted in each detail aid were numerous slides titled 'SAFETY INFORMATION FROM A COMPREHENSIVE CLINICAL TRIAL PROGRAMME',(including slide 18/47 and 22/47 for Nilemdo and Nustendi, respectively, in the short sales aid and slides 51/86 and 55/86 in the long sales aid). Within a section of these slides under the subheading 'CONCOMITANT SIMVASTATIN', reference was made to concomitant use with simvastatin > 40mg daily being contraindicated.

The Panel noted besides the prescribing information sections of each sales aid, slide 7/47 of the short sales aid and 18/86 of the long sales aid and the slides titled 'SAFETY INFORMATION FROM A COMPREHENSIVE CLINICAL TRIAL PROGRAMME' referenced above, the only other mention of the simvastatin contraindication appeared to be on slide 75/86 of the long sales aid (ref BEM/21/0828) which was headed:

> 'ADD NILEMDO® OR NUSTENDI® TO OTHER LLTS TO HELP UNCONTROLLED PATIENTS ACHIEVE THEIR LDLC GOALS' and directly below in slightly smaller font it stated 'CONCOMITANT USE WITH SIMVASTATIN > 40 MG IS CONTRAINDICATED; PLEASE REFER TO THE SMPC FOR USE WITH STATINS'.

The Panel noted its comments and rulings in Case AUTH/3504/4/21, including that the contraindication with simvastatin >40mg daily needed to be immediately apparent to health professionals in promotional material, which referred to adding on to existing oral lipid lowering

treatments. The Panel noted the undertaking in this regard was signed on 6 December 2021 by Daiichi Sankyo.

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 existing oral lipid-lowering treatments or a statin. The Panel, noting certain slides specifically made reference to therapeutic use of Nilemdo and Nustendi in combination with a statin (including slides 3 and 8 of the short sales aid and slides 1, 8, 13, 20, 28, 30, 34 and 46 of the long sales aid), considered that those slides should have made the contraindication in patients taking simvastatin >40mg daily immediately apparent to readers and they did not.

The Panel noted that representatives had the option of accessing any slide from the menu bar and therefore each slide needed to stand alone in relation to the requirements of the Code. In the Panel's view, reference to the contraindication with simvastatin > 40mg on subsequent slides was not sufficient to negate the misleading impression given that Nilemdo and Nustendi could be used in combination with any dose of any statin, which was not so; the Panel therefore ruled a **breach of Clause 6.1** in relation to each sales aid (refs BEM/21/0826 and BEM/21/0828).

The Panel noted that the complainant had alleged a breach of Clause 6.2 and, in this regard, considered that the implied allegation was that the material did not make it clear to prescribers that Nilemdo and Nustendi should not be used in combination with a simvastatin dosage >40mg and this misleading impression could not be substantiated. The Panel therefore ruled a **breach of Clause 6.2** in relation to each sales aid (refs BEM/21/0826 and BEM/21/0828).

Briefing materials

With regard to briefing materials, the Panel considered the associated briefing documents for the long sales aid (ref BEM/21/0828) and short sales aid (ref BEM/21/0826) ruled upon above; the briefing document for the long sales aid was BEM/21/0829, January 2022 and the briefing document for the short sales aid was BEM/21/0827, December 2021. The Panel noted that the first slide of both briefing documents included the indications of Nilemdo and Nustendi in very small font in the footer of the slide but reference to the information in Sections 4.2, 4.3 and 4.4 of the SPCs in relation to concomitant use with statins was omitted from both.

Short sales aid briefing document (ref BEM/21/0827)

In relation to the short sales aid briefing document, the Panel noted the first substantive slide which followed the contents slide (slide 4/22) was titled 'THE NILEMDO AND NUSTENDI SHORTY eCA OVERVIEW' and stated that 'Market research has shown that there is great excitement and anticipation from HCPs about the launch of simple-to-take oral products, which can be added to other LLTs to help their uncontrolled patients get closer to their LDL-C goals. It is really important to simply translate the excitement and highlight the differences NILEMDO and NUSTENDI can make in bringing down elevated LDL-C and tell a very simple but compelling narrative.'. It further stated 'Within market research and the KOL think tank, prescribers confirmed that a key benefit of NILEMDO and NUSTENDI is the "add on" oral treatment. HCPs believe that it is much more effective to add on a treatment than to increase the dose of an existing treatment'. From slide 9/22 the briefing covered a page-by-page overview of the short

detail aid. Slide 11/22 of the short sales aid briefing document under the heading 'KEY TAKEAWAYS' stated 'Patients that remain uncontrolled on current therapies require additional LLTs to reach their LDL-C goals are the patient group you wish to focus on in your CONVERSATION' and encouraged representatives to 'FOCUS the conversation on your TARGET PATIENT population (Patients that remain uncontrolled on current therapies and require additional LLTs to reach their LDL-C goals)'. In the Panel's view, such reference within briefing material for a promotional sales aid for Nilemdo and Nustendi encouraged the promotion of the addition of these two medicines to current LLTs therapy but no reference was made to the contraindication with simvastatin > 40 mg.

In relation to Slide 7/47 of the short sales aid described above, Slide 12/22 of the short sales aid briefing document (ref BEM/21/0827) under a heading 'ADDITIONAL INFORMATION' stated 'Nilemdo and Nustendi can be added to existing oral LLTs...' and that 'HCPs are most likely to consider treatment with NILEMDO or NUSTENDI in high- or very-high-risk patients who are uncontrolled on maximally tolerated statins or other LLTs'. The contraindication with simvastatin >40 mg, although included in the corresponding short sales aid slide (7/47), was not highlighted in the associated briefing document in relation to that slide.

The contraindication was, however, mentioned on slide 17/22 of the short sales aid briefing document (ref BEM/21/0827) which was subtitled in prominent red font 'SPECIAL WARNINGS'. This slide of the briefing was in relation to the slides from the short sales aid titled 'SAFETY INFORMATION FROM A COMPREHENSIVE CLINICAL TRIAL PROGRAMME' as referred to above (slides 18, 20, 22 and 24). The contraindication also appeared on slide 20/22 of the same briefing document, subtitled 'SAFETY INFORMATION', within the 'ADDITIONAL INFORMATION' section and which related to one of the slides of the short detail aid headed 'SAFETY INFORMATION FROM A COMPREHENSIVE CLINICAL TRIAL PROGRAMME'. The Panel further noted that Slide 15/22 of the short sales aid briefing document stated 'The full details of the efficacy data and clinical trial programme are not provided in the short eCA, but the below information will be useful context [if] case of any queries. You can always refer to the ICA for further information'. It then listed the clinical trials including 'CLEAR Wisdom' and 'CLEAR Harmony' in which Nilemdo was added to maximally-tolerated statin (which could be no statin) +/- other LLTs. Slide 16/22 referred to 'Study 053' in which Nustendi was added to maximally-tolerated statin (which could be no statin). Both slides described the significant LDL-C reductions seen in these trials. Neither slide referred to the contraindication with simvastatin > 40mg.

Within the short sales aid briefing document, the first mention of the contraindication was not until slide 17/22 under the 'KEY TAKEAWAYS' section for that slide and the contraindication was similarly described again on slide 20/22; both slides correlated to the slides of the short detail aid titled 'SAFETY INFORMATION FROM A COMPREHENSIVE CLINICAL TRIAL PROGRAMME' as described above. It appeared to the Panel from the short sales aid briefing document that representatives were only briefed to discuss the relevant contraindication in relation to certain safety slides rather than whenever discussing the use of Nilemdo and Nustendi in combination with a statin.

Long sales aid briefing document (ref BEM/21/0829)

The Panel noted that similar concerns applied in relation to the briefing document for the long sales aid. The Panel noted the first actual slide of the long sales aid briefing document which followed the contents slide, slide 4/36 was titled 'INTRODUCING NILEMDO AND NUSTENDI'

and stated 'NILEMDO® (180 mg bempedoic acid) and NUSTENDI® (180 mg bempedoic acid + ezetimibe 10 mg) are oral options that contain bempedoic acid which has a novel mechanism of action. They can be added to existing oral LLTs to help deliver the additional LDL-C reductions that uncontrolled patients need'. This was followed by the contraindication with simvastatin > 40 mg in smaller font.

The next slide of the long sales aid briefing document, slide 5/36 was titled 'NILEMDO AND NUSTENDI STRATEGY AND BRAND POSITIONING', asked the question 'Who are the patients we can leverage?' which was followed by 'Patients with high and very high cardiovascular (CV) risk (uncontrolled) currently treated with optimised oral LLTs (max. tolerated statin + ezetimibe)'. An additional heading on the same slide, 'Positioning', included that '**NILEMDO or NUSTENDI is an add-on treatment for uncontrolled patients at high/very high risk after optimised oral LLTs**. NILEMDO and NUSTENDI do not replace other oral LLTs (e.g statins) but may be added to existing oral therapies for more effective LDL-C lowering. Add on NILEMDO or NUSTENDI after maximally tolerated statins and ezetimibe before PCSK9is in uncontrolled patients'.

The Panel noted that similar to the short sales aid briefing document, slide 12/36 of the long sales aid briefing document (ref BEM/21/0829) was titled 'The NILEMDO AND NUSTENDI ICA OVERVIEW' and stated that 'Market research had shown that there was great excitement and anticipation from HCPs about the launch of simple-to-take oral products which can be added to other LLTs to help their uncontrolled patients get closer to their LDL-C goals. It is really important to simply translate the excitement and highlight the differences NILEMDO and NUSTENDI can make in bringing down elevated LDL-C and tell a simple but compelling narrative.' and 'Within market research and the KOL think tank, prescribers confirmed that a key benefit of NILEMDO and NUSTENDI is the 'add on' oral treatment. HCPs believe that it is much more effective to add on a treatment that to increase the dose of an existing treatment'.

In the Panel's view slides 5/36 and 12/36 of the long sales aid briefing document encouraged the promotion of the addition of Nilemdo and Nustendi to current LLTs therapy but no reference was made to the contraindication with simvastatin > 40 mg. In this regard, the Panel noting its comments above in relation to the short sales aid briefing document considered that the reference to adding to existing oral LLTs and maximally tolerated statins should have been accompanied by a reference to the contraindication with simvastatin > 40mg.

The Panel noted slides 17 to 34 of the long sales aid briefing document covered a page by page overview of the long sales aid and in this regard, the Panel noted its ruling of a breach of Clause 6.1 above in relation to the long sales aid, particularly in relation to slides that referred to Nilemdo and Nustendi indications in combination with other LLTs or statins without reference to the contraindication with simvastatin >40mg.

Slide 19/36 of the long sales aid briefing document which correlated to slide 8/86 of the long sales aid was sub titled 'UNMET NEED' in red and on this slide beneath the heading 'KEY TAKEAWAYS' it stated 'Most patients remain uncontrolled on current therapies and require additional LLTs to reach their LDL-C goals' and beneath the heading 'ADDITIONAL INFORMATION' on the same slide it stated that 'Most hypercholesterolaemia patients (80%) remain uncontrolled on statins, which puts them at greater CV risk' followed by 'In order to reach their LD-C goals, uncontrolled patients require additional LLTs (on top of current therapies)'. Slide 20/36 of the long sales aid briefing document which correlated to the Guidelines section of the long sales aid included as the 'KEY TAKEAWAYS' that 'The guidelines recommend that

uncontrolled patients need additional LLTs to reach LDL-C goals and reduce their CV risk'. The Panel noted that neither slides 19 or 20 of the long sales aid briefing document or the associated slides of the long sales aid made reference to the contraindication with simvastatin > 40mg.

Slide 21/36 of the briefing document, which correlated to the 'ADD ON NILEMDO OR NUSTENDI TO TAKE BACK CONTROL' slide (18/86) of the long detail aid which referred to the contraindication of the concomitant use of Nilemdo and Nustendi with simvastatin > 40mg appeared to make no reference to the contraindication on the correlating slide of the briefing document itself. The briefing document instead included under the heading 'ADDITIONAL INFORMATION' that 'NILEMDO® and NUSTENDI® can be added to existing oral LLTs or given as monotherapy in patients who are intolerant to statins or where statins are contraindicated' and 'HCPs are most likely to consider treatment with NILEMDO® or NUSTENDI® in high-or very-high-risk patients who are uncontrolled on maximally tolerated statins or other LLTs'. In the Panel's view the failure to highlight the contraindication when briefing representatives on a slide of the detail aid that included the contraindication underplayed its importance; it might convey the impression that the contraindication was not an important message to convey from that slide.

Slides 23, 25, and 28 of the long sales aid briefing document correlated to the slides of the detail aid on clinical trials and included reference to addition of Nilemdo and Nustendi to maximally-tolerated statins in CLEAR Wisdom, CLEAR Harmony and Study 053 but the slides of the briefing document, similarly to the slides of the long detail aid did not refer to the contraindication with simvastatin > 40mg.

The Panel noted Slide 29/36 of the long sales aid briefing document which correlated to the slides of the detail aid titled 'SAFETY INFORMATION FROM A COMPREHENSIVE CLINICAL TRIAL PROGRAMME' included 'KEY TAKEAWAYS' which stated:

- Concomitant use with simvastatin >40 mg is contraindicated for both NILEMDO® and NUSTENDI®
- Before prescribing, physicians should consider all contraindications and precautions
- When NILEMDO® or NUSTENDI® is coadministered with simvastatin, the simvastatin dose should be limited to 20 mg daily (or 40 mg daily for patients with severe hypercholesterolaemia and who are at high risk for CV complications, who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks)

The 'ADDITIONAL INFORMATION' section on Slide 32/36 of the long sales aid briefing document which correlated to one of the slides of the detail aid titled 'SAFETY INFORMATION FROM A COMPREHENSIVE CLINICAL TRIAL PROGRAMME' further stated:

With both 'NILEMDO® and NUSTENDI®:

- Concomitant use with simvastatin > 40 mg is contraindicated. When NILEMDO® or NUSTENDI® is coadministered with simvastatin, the simvastatin dose should be limited to 20 mg daily (or 40 mg daily for patients with severe hypercholesterolaemia and who are at high risk for CV complications, who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks)

Whilst the contraindication was referred to on slide 4/36 of the long sales aid briefing document titled 'INTRODUCING NILEMDO AND NUSTENDI', it next appeared on Slide 29/36 subtitled 'SPECIAL WARNINGS' within the 'KEY TAKEAWAYS' section and on Slide 32/36 subtitled 'SAFETY INFORMATION' within the 'ADDITIONAL INFORMATION' section. Both Slides of the long sales aid briefing document (29/36 and 32/36) related to slides of the long detail aid titled 'SAFETY INFORMATION FROM A COMPREHENSIVE CLINICAL TRIAL PROGRAMME'. The Panel was concerned that when the contraindication was mentioned it was primarily on the safety pages and thus might imply to representatives that the contraindication should only be mentioned in that context.

The Panel noted Clause 17.9 stated, amongst other things, that representatives briefing material must comply with the relevant requirements of the Code and must not advocate, either directly or indirectly, any course of action which would be likely to lead to a breach of the Code; companies must prepare detailed briefing material for medical representatives on the technical aspects of each medicine which they will promote.

The Panel noted its observations above in relation to the short sales aid briefing document (ref BEM/21/0827) and long sales aid briefing document (ref BEM/21/0829) and queried why information regarding the contraindication with simvastatin > 40mg was not provided within these briefing documents on the slides highlighted (Slides 4, 11, 12, 15, and 16 of the short sales aid briefing document and Slides 5, 12, 19, 20, 23, 24, 25 and 28 of the long sales aid briefing document).

In the Panel's view, noting the contents of both briefing documents, it was not made sufficiently clear within each briefing document that Nilemdo and Nustendi could not be used in combination with simvastatin > 40mg, whenever there was reference to combination with statins or other LLTs. The Panel, noting its comments above, considered that representatives had not been given clear briefing on the contraindications with simvastatin and the need to mention it when making claims about combining Nilemdo and Nustendi with other cholesterol lowering agents as alleged and a **breach of Clause 17.9** was ruled in relation to both the short (BEM/21/0827) and long sales aid briefing documents (BEM/21/0829).

Leavepieces

The Panel noted Daiichi Sankyo provided two leavepieces (ref BEM/21/0653, December 2021 and BEM/21/0816 January 2022).

The Panel noted the first page for BEM/21/0653 was headed 'IN THE STRUGGLE AGAINST ELEVATED LDL-C, ADD ON TO BRING DOWN' with an image of a woman and her doctor pulling what appeared to be cholesterol into a hole and the Nilemdo and Nustendi logos with the strapline 'Add on to take back control'. This was followed by the indications for both medicines in small font but without reference to the information in Sections 4.2, 4.3 and 4.4 of the SPCs in relation to concomitant use with statins. The second page was titled 'CVD IS RESPONSIBLE FOR 1 IN 4 DEATHS IN ENGLAND, EQUATING TO 1 IN EVERY 3 MINUTES' followed by 'Around 80% of ASCVD patients using moderate or high intensity statins are not reaching the LDL-C treatment goal of < 1.8mmol/L, and remain at increased risk of CV events'. This was followed by 'Additional LLTs are needed to complement current therapies to help uncontrolled patients achieve their LDL-C goals' below which in bolder blue font it stated 'NILEMDO and NUSTENDI are oral options that contain bempedoic acid which has a novel mechanism of

action. They can be added to existing oral LLTs to help deliver the additional LDL-C reductions that uncontrolled patients need' followed directly by 'Concomitant use with simvastatin > 40mg is contraindicated; please refer to the SmPC for use with statins' in slightly smaller font. The title of the third page was 'ADD NILEMDO OR NUSTENDI TO OTHER LLTS TO HELP UNCONTROLLED PATIENTS ACHIEVE THEIR LDL-C GOALS' which was followed directly by 'CONCOMITANT USE WITH SIMVASTATIN > 40MG IS CONTRAINDICATED; PLEASE REFER TO THE SMPC FOR USE WITH STATINS' in slightly smaller, less bold font. The fourth page stated 'WHEN YOU AND YOUR PATIENTS ARE FIGHTING TO TAKE BACK CHOLESTEROL CONTROL, ADD ON ORAL, ONCE-DAILY NILEMDO OR NUSTENDI'. The final two pages included the references and the Nilemdo and Nustendi prescribing information.

The first page of the leavepiece BEM/21/0816 stated that it was Nilemdo and Nustendi local guidance and included an image of a map of the UK. The indications for Nilemdo and Nustendi were included to the right of the image of the map but without reference to the information in Sections 4.2, 4.3 and 4.4 of the SPCs in relation to concomitant use with statins. The second page discussed that Nilemdo and Nustendi had been added to the local formulary for use in primary and secondary care and that bempedoic acid with ezetimibe was recommended by NICE as an option for treating primary hypercholestrolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet in adults but stated that it was only recommended if statins were contraindicated or not tolerated. In the Panel's view there was thus no need to include the contraindication with simvastatin > 40mg in this regard. The third page was headed 'IN THE STRUGGLE AGAINST ELEVATED LDL-C, ADD ON TO BRING DOWN' followed by 'Add NILEMDO or NUSTENDI to other LLTs to help uncontrolled patients achieve their LDL-C goals. Concomitant use with simvastatin > 40mg is contraindicated; please refer to the SmPC for more information'. The fourth page stated 'WHEN YOU AND YOUR PATIENTS ARE FIGHTING TO TAKE BACK CONTROL, ADD ON ORAL, ONCE-DAILY NILEMDO OR NUSTENDI'. The final two pages included the references and the Nilemdo and Nustendi prescribing information.

The Panel was concerned that the first page of each leavepiece included the indication of Nilemdo and Nustendi without reference to the information in Sections 4.2, 4.3 and 4.4 of the SPC in relation to concomitant use with statins as per the Nilemdo and Nustendi SPC.

The Panel considered that the fourth page of each leavepiece referred to adding on oral, once daily Nilemdo or Nustendi in relation to cholesterol control and in that regard implied addition of the two medicines to current LLTs. In the Panel's view and, on balance, 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 existing oral lipid lowering treatments or a statin. The Panel considered that representatives had the option of detailing any page of the leavepiece and therefore each page needed to stand alone in relation to the requirements of the Code. In the Panel's view, the failure to refer to the contraindication with simvastatin > 40mg on the first and fourth pages of each leavepiece gave the misleading impression that Nilemdo and Nustendi could be used in combination with any dose of simvastatin which was not so. Reference to the contraindication on the other pages was not sufficient to negate the misleading impression and the Panel therefore ruled a **breach of Clause 6.1** in relation to each leavepiece.

The Panel noted that the complainant had alleged a breach of Clause 6.2 and in this regard considered that the implied allegation was that the material did not make it clear to prescribers

that Nilemdo and Nustendi should not be used in combination with a simvastatin dosage greater than 40mg and this misleading impression could not be substantiated. The Panel therefore ruled a **breach of Clause 6.2** in relation to each leavepiece.

Training

With regard to the alleged lack of training on the contraindications around simvastatin, the Panel noted Daiichi Sankyo's submission that that its sales representatives went through an extensive initial training course upon joining the company, which contained specified training allocations on product SPCs and were required to do an SPC validation test. Daiichi Sankyo submitted training was inclusive of all safety warnings and contraindications.

In this regard, the Panel noted Daiichi Sankyo provided an SmPC validation test (BEM/20/0135; June 2020) which included the multiple choice questions 'What are the prescribing considerations when Nilemdo is coadministered with simvastatin therapy?' and listed when Nilemdo is co-administered with simvatstain, simvastatin dose should be limited to 40mg daily (or 80mg daily for patients with severe hypercholesterolaemia and high risk for cardiovascular complications, who have not achieved their treatment goals on lower doses and when the benefits are expected to outweigh the potential risks) and 'What are the contraindications for Nilemdo?' which listed concomitant use with simvastatin > 40 mg daily as an option. The Panel noted that there did not however appear to be similar questions in relation to Nustendi.

The Panel noted that this allegation related to general training activities rather than the specific briefing materials considered and ruled in breach of the Code above. The Panel considered, based on the evidence before it, that it had not been established that sales representatives had not been trained properly on mandatory contraindications around simvastatin as alleged and therefore ruled **no breach of Clause 17.1.**

Representatives' sales calls

The Panel noted that the complainant provided no details in relation to any specific sales calls. The Panel noted its concerns about the briefing materials above and the rulings of breaches of the Code in relation to the omission of the reference to the contraindication with simvastatin >40 mg on certain slides of the two briefing documents. The Panel considered that in such circumstances it was not unreasonable to query whether what was said by representatives reflected the briefing materials which had been ruled in breach of the Code on this point. Nonetheless, the Panel noting that the complainant had not detailed specific sales calls considered on this very narrow ground that it had not been established that sales representatives did not make clear reference to the contraindication with simvastatin >40mg during sales calls as alleged and, on balance, **no breach of Clause 6.1** was ruled.

Overall

The Panel noted its rulings of breaches of Clauses 6.1, 6.2 and 17.9 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 the therapeutic use in combination with a statin/other LLTs, without sufficiently mentioning that Nilemdo and Nustendi were contraindicated with simvastatin>40mg in each of the sales aids, leavepieces

and briefing materials, 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. In addition, the Panel was concerned that when apparently reproducing the indications in both sales aids, both briefing documents and leavepieces, the reference to Sections 4.2, 4.3, and 4.4 of the SPCs were omitted. The Panel was particularly concerned in relation to briefing material for the long sales aid when at Slide 21/36 it omitted to instruct representatives to highlight the contraindication on an associated slide in the long sales aid (slide 18/86) that contained the contraindication thereby underplaying its importance and giving the impression that the contraindication was not an important message to convey. Patient safety was of the utmost importance. The Panel noted that a number of concerns had been raised across a number of materials and breaches of the Code had been ruled. The Panel considered therefore that the repeated failure to comply with the Code on this matter was particularly serious and 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 **7 July 2022**

Case completed **25 October 2023**