**Case AUTH/3770/5/23**

# COMPLAINANT v DAIICHI SANKYO

## Allegations regarding the promotion of Nustendi on a website

### CASE SUMMARY

**This case was in relation to the omission of a contraindication statement that Nustendi (bempedoic acid and ezetimibe) coadministered with a statin was contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases from three webpages of a promotional website.**

**The outcome under the 2021 Code was:**

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| **Breach of Clause 2** | **Bringing discredit upon, and reducing confidence in, the pharmaceutical industry** |
| **Breach of Clause 5.1** | **Failing to maintain high standards** |
| **Breach of Clause 6.1** | **Providing misleading information** |
| **Breach of Clause 6.2** | **Providing misleading information that was incapable of substantiation** |

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| **No Breach of Clause 2 (x2)** | **Requirement that activities or materials must not bring discredit upon, or reduce confidence in, the pharmaceutical industry** |
| **No Breach of Clause 5.1 (x2)** | **Requirement to maintain high standards** |
| **No Breach of Clause 6.1 (x2)** | **Requirement that information must be accurate, up-to-date and not misleading** |
| **No Breach of Clause 6.2 (x2)** | **Requirement that claims/information/comparisons must be capable of substantiation** |

**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 complainant, who since became non-contactable, about Daiichi Sankyo UK Ltd.

### COMPLAINT

The complaint wording is reproduced below:

> "This complaint is around Nustendi promotional claims. There are a number of claims on a Nustendi promotional website, whereby it is suggested Nustendi can be added to other statins without information provided about a key contra-indication mentioned within the

Nustendi SPC, that required consideration when Nustendi was added to patients who were also on statin therapy. A contraindication within the Nustendi SPC is - [Nustendi coadministered with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases].

On the home page of the Nilemdo-Nustendi promotional website [ BEM/22/0035 Date of preparation: September 2022], there were a few claims about adding Nustendi to other statins. A claim read - 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. However, the core contraindication that addition of Nustendi to a statin should not occur if a patient had active liver disease or unexplained persistent elevations in serum transaminases was not provided. A busy healthcare professional with finite time viewing this claim, would assume that it is reasonable to add Nustendi to other statin therapies without having the contra-indication written next to the claim on the page. The indication of Nustendi was also provided on the page which mentioned adding to statins, but the supporting information about the contra-indication in liver disease or unexplained persistent elevations in serum transaminases when patients were already on statin was not provided next to the indication. This was concerning as statins are used widespread in high cholesterol management, so such an important contraindication should have been provided on the page. As this was a patient safety risk - [Breach clauses 6.1, 6.2, 5.1 and 2].

On the efficacy part of the website [Job Code: BEM/22/0035 | Date of preparation: September 2022], a list of clinical trials were presented towards the end of the page, which referred to Nustendi added to maximally tolerated statin therapy. The impression to a healthcare professional with finite time would be that it is reasonable to add Nustendi to other statin therapies without realising the contra-indications around the elevation in transaminases or liver disease. This was also a breach in patient safety considerations - [Breach clauses 6.1, 6.2, 5.1 and 2].

On the tolerability page of the website [ BEM/22/0035 | Date of preparation: September 2022], a section towards the bottom of the page was titled Safety information from a comprehensive clinical trial programme. Below this heading were 2 boxes listing contra-indications and special warnings and precautions and below this information was an image of 2 individuals pulling a rope. In the contra-indications section of the box for Nustendi, there was only reference to 4 out of the 5 contra-indications listed in the Nustendi SPC. The one that was missing was Nustendi coadministered with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases. It was unbalanced to not provide such a vital contra-indication and nor was there any reason required to omit this particular contraindication considering other contraindications were given. [Breach clauses 6.1, 6.2, 5.1 and 2].

It is important to note that not all HCPs can be considered experts in prescribing and being aware of contra-indications for Nustendi. If such claims were made about addition of Nustendi to a statin which was common practice, it was really important to provide the required contra-indication around liver disease and elevations in transaminases considerations when adding to a statin rather than assumptions."

When writing to Daiichi Sankyo, the Authority asked it to consider the requirements of Clauses 6.1, 6.2, 5.1 and 2 of the 2021 Code as cited by the complainant.

**RESPONSE**

The response from Daiichi Sankyo is reproduced below:

> "Daiichi Sankyo UK (DSUK) takes its obligations under the ABPI Code of Practice seriously, strives to maintain high standards and always behave responsibly and ethically and we are disappointed to receive this complaint.
>
> This letter is the DSUK formal response to the alleged breaches.
>
> **Complainant allegation 1**
>
> The complainant is concerned about the website nilemdo-nustendi.co.uk; they state that the home page and "Efficacy" section make claims in relation to adding Nustendi and Nilemdo to other lipid-lowering therapies (LLTs) without referring to the contraindication listed in the Nustendi Summary of Product Characteristics (SmPC) of coadministered with a statin in patients with active liver disease or unexplained persistent elevations in serum transaminases.
>
> **Daiichi Sankyo response 1**
>
> The indication for Nustendi is for the treatment of 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 [1]
>
> The statements on the home page and "Efficacy" section of the website accurately reflect the indication for Nustendi and we do not consider that in this context specific reference to a contraindication in patients with hepatic impairment is necessary. Prescribers of any medicine will be cautious in this special population, given the role of the liver in drug metabolism, and both sections of the website refer the reader to the SmPC for more information. In addition, the contraindication is listed clearly in the prescribing information.
>
> Our position in relation to this was reinforced by a recent ruling in Case AUTH/3649/5/22 in which the Panel stated:
>
> > '*In relation to the contra-indication for Nustendi when co-administered with a statin in patients with active liver disease or unexplained persistent elevations in serum transaminases, the Panel considered that the body of the material did not imply that there would be no considerations in relation to patients with liver disease; health*

*professionals would likely be cautious when prescribing to such patients and the contraindication was stated in the prescribing information*'

It is also worth noting that, although statins may be widely used in the management of hypercholesterolaemia generally, that is not the case in this special population, given that statins are contraindicated in patients with active liver disease or unexplained persistent elevations in transaminases.

With the above in mind, we do not consider that the claims included in these sections of the website at issue are misleading and we deny any breach of Clause 6.1. Further the claims reflect the indication for Nustendi, are capable of substantiation and we refute any breach of Clause 6.2 in that regard. Given the above we do not consider that there has been any breach of Clauses 5.1 and 2.

**Complainant allegation 2**

The complainant has raised a concern that the 'Tolerability' section of the same website lists the contraindications for Nustendi but omits the contraindication of co-administration with a statin in patients with active liver disease or unexplained persistent elevations in serum transaminases.

**Daiichi Sankyo response 2**

The complainant is correct; this contraindication was missing from this section of the website. This was due to an oversight during the approval process. The matter is being managed via our deviation process, we will investigate the root cause and appropriate corrective and preventive actions will be put in place, as appropriate. In the meantime, the website has since been taken down.

Given the omission, we acknowledge that this page of the website was misleading in relation to the contraindications for Nustendi, inaccurate and not capable of substantiation, in breach of Clauses 6.1 and 6.2. We also acknowledge that this amounts to a failure to maintain high standards, contrary to the requirements of Clause 5.1.

DSUK is extremely disappointed that this could have occurred, and we apologise for this matter.

On the page in question, under contra-indications for Nustendi in particular , the reader is directed to the SmPC for statins by the statement "*When NUSTENDI is co-administered with a statin, please refer to the Summary of Product Characteristics for that particular statin therapy*". Further, as noted above, statins are contra-indicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

In addition to this, on the same page that references the contraindications and special warnings/precautions for use for Nustendi, there is a statement referring the reader to the Nustendi SmPC before prescribing.

For these reasons we do not consider that the omission of the contraindication in these circumstances amounts to a breach of Clause 2."

## PANEL RULING

The complaint related to the omission of the contraindication statement that Nustendi (bempedoic acid and ezetimibe) coadministered with a statin was contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases from certain webpages of a Nilemdo (bempedoic acid) and Nustendi promotional website (BEM/22/0035, certified September 2022).

The Panel noted the complainant referred to three webpages: the homepage, efficacy page and tolerability page. The header of each webpage contained the Nilemdo and Nustendi brand logos along with the menu headings 'Home', 'Mechanism of Action', 'Efficacy, 'Tolerability', 'Dosing', 'Resources' and 'Prescribing Information'.

The Panel made its rulings on each webpage accordingly.

### Homepage

The Panel noted the homepage included the large claim 'When you and your patients are fighting to take back cholesterol control, add on oral, once-daily NILEMDO or NUSTENDI', beneath which in smaller font was the text 'Concomitant use with simvastatin >40 mg is contraindicated; please refer to the SmPC for more information'. The homepage included a section for Nilemdo and Nustendi's therapeutic indications which had prominent links to prescribing information, and sections titled 'LDL-C goals' and 'About Nilemdo and Nustendi'.

The Panel noted the section titled 'About Nilemdo and Nustendi' included the claim 'Add on Nilemdo or Nustendi to take back control' beneath which was the statement '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 [lipid-lowering therapies] to help deliver the additional LDL-C reductions that uncontrolled patients need. Concomitant use with simvastatin >40mg is contraindicated; please refer to the SmPC for more information.'

The Panel noted the complainant's allegation that there were claims about adding Nustendi to statins but that the contraindication when co-administered with a statin in patients with active liver disease or unexplained persistent elevations in serum transaminases was not stated. The complainant was concerned that statin use was widespread in high cholesterol management, so such an important contraindication should have been provided on the page.

The Panel took account of Daiichi Sankyo's submission that although statins may be widely used in the management of hypercholesterolaemia generally, that was not the case in this special population, given that statins were contraindicated in patients with active liver disease or unexplained persistent elevations in transaminases.

In the Panel's view, the purpose of the homepage was to provide an overview and direct users to further detailed information as needed. The Panel considered that the content of the homepage did not imply that there would be no considerations in relation to patients with active liver disease or unexplained persistent elevations in serum transaminases. Health professionals would likely exercise caution when prescribing to this patient population and refer to a more relevant webpage on the website.

Noting the content and purpose of the homepage, the Panel considered that the complainant had not established that the omission of the contraindication statement 'Nustendi coadministered with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases' meant that the homepage was misleading as alleged. **No breach of Clause 6.1** was ruled.

The Panel noted the complainant bore the burden of proof. The Panel considered that the complainant had not established that the homepage was not capable of substantiation and **no breach of Clause 6.2** was ruled.

The Panel noted its rulings of no breaches above and ruled **no breach of Clause 5.1 and 2** accordingly.

**Efficacy page**

The Panel noted the efficacy page included the large claim 'NILEMDO and NUSTENDI: Add on to take back control', beneath which in smaller font was the text 'Concomitant use with simvastatin >40 mg is contraindicated; please refer to the SmPC for more information'. The webpage included a section with data on each medicine's LDL-C reduction beneath which was a section titled 'Robust clinical trial programme including a broad range of patient subgroups' that contained the results of various trials. The page included prominent links to the Nilemdo and Nustendi prescribing information.

The complainant alleged that the clinical trial programme section, which referred to Nustendi added to maximally tolerated statin therapy, did not make clear that Nustendi co-administered with a statin was contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

The Panel took account of Daiichi Sankyo's submission that statins were contraindicated in patients with active liver disease or unexplained persistent elevations in transaminases.

The Panel considered the immediate and overall impression of the efficacy page to a health professional. In the Panel's view, readers would expect the efficacy page to have included data which focussed on the clinical outcomes of Nilemdo and Nustendi, based on trial data.

The Panel considered that the content of the efficacy page did not imply that there would be no considerations in relation to patients with active liver disease or unexplained persistent elevations in serum transaminases. Health professionals would likely exercise caution when prescribing to this patient population and refer to a more relevant page on the website.

Noting the content and purpose of the efficacy page, the Panel considered that the complainant had not established that the omission of the contraindication statement 'Nustendi coadministered with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases' on the efficacy webpage meant it was misleading as alleged. **No breach of Clause 6.1** was ruled.

The Panel noted the complainant bore the burden of proof. The Panel considered that the complainant had not established that the efficacy webpage was not capable of substantiation and **no breach of Clause 6.2** was ruled.

The Panel noted its rulings of no breaches above and ruled **no breach of Clauses 5.1 and 2** accordingly.

**Tolerability page**

The Panel noted the tolerability page included the large claim 'NILEMDO and NUSTENDI: Generally well tolerated in clinical studies' and included sections pertaining to adverse events/reactions, contraindications and special warnings and precautions.

The complainant alleged that in the contraindications section for Nustendi, there was reference to only four out of the five contraindications listed in the Nustendi SPC. In this regard, the Panel noted the section of the webpage at issue included the subheading 'Concomitant Simvastatin', which detailed the contraindication of concomitant use with simvastatin >40mg daily, and the subheading 'Other Contraindications' which listed:

- 'Hypersensitivity to the active substance or to any of the excipients
- Pregnancy
- Breastfeeding
- When NUSTENDI is coadministered with a statin, please refer to the Summary of Product Characteristics for that particular statin therapy'.

The Panel noted that the contraindication from section 4.3 of the Nustendi SPC regarding coadministration with a statin in patients with active liver disease or unexplained persistent elevations in serum transaminases was missing from the webpage.

The Panel noted Daiichi Sankyo's acknowledgment that this was due to an oversight during its approval process.

The Panel considered the immediate and overall impression of the tolerability page to a health professional. While the Panel noted its view above that health professionals would likely exercise caution when prescribing to patients with active liver disease or unexplained persistent elevations in serum transaminases, the Panel considered that readers would have expected the tolerability webpage in question to contain a complete list of contraindications. The Panel did not have the webpage containing prescribing information before it. Nonetheless, the Panel considered that the tolerability page could not rely on qualification within the prescribing information, hosted on another webpage, to negate the misleading impression given that the list of contraindications provided on the tolerability page was complete. Listing all but one contraindication on the tolerability page was misleading and the Panel ruled a **breach of Clause 6.1** as acknowledged by Daiichi Sankyo.

The Panel considered that the misleading impression given that the tolerability page contained a complete list of Nustendi contraindications was incapable of substantiation. **A breach of Clause 6.2 was ruled** as acknowledged by Daiichi Sankyo.

The Panel considered that health professionals should be able to rely on company produced material to be complete, accurate and unambiguous. The Panel considered that the misleading impression given that the list of contraindications on the tolerability page was complete meant that Daiichi Sankyo had failed to maintain high standards and **a breach of Clause 5.1 was ruled**.

Clause 2 was a sign of particular censure and was reserved for such use.

The Panel took account of Daiichi Sankyo's submission that statins were contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases and noted the reader was directed to consult the relevant statin SPC 'when Nustendi is coadministered with a statin'. In any instance, the Panel considered that the Nustendi tolerability page should stand alone with regard to the requirements of the Code and should not rely on the reader consulting another company's SPC to negate a misleading impression given about Nustendi. It was crucial that health professionals and others could rely completely upon the industry for accurate and complete information about their medicines, including contraindications, the omission of which could potentially impact patient safety.

The Panel considered that the omission of the contraindication regarding coadministration with a statin in patients with active liver disease or unexplained persistent elevations in serum transaminases, on a section of the website which was intended to inform health professionals about Nustendi contraindications, meant, on balance, that Daiichi Sankyo had reduced confidence in, and brought discredit upon, the pharmaceutical industry and the Panel **ruled a breach of Clause 2**.

**Complaint received** **29 May 2023**

**Case completed** **9 July 2024**