CASES AUTH/3565/10/21 and AUTH/3566/10/21

VOLUNTARY ADMISSION BY OTSUKA EUROPE AND OTSUKA UK

Incorrect prescribing information and a breach of undertaking

Otsuka Pharmaceutical Europe Limited (Case AUTH/3565/10/21) and Otsuka Pharmaceuticals (UK) Limited (Case AUTH/3566/10/21) submitted a joint voluntary admission in relation to the omission of the frequency of dosing for the monthly intramuscular injection formulation from the prescribing information for Abilify/Abilify Maintena (aripiprazole) and in relation to a breach of undertaking.

The prescribing information at issue was approved and used by both Otsuka Europe and Otsuka UK therefore the voluntary admission was made jointly by both organisations.

Otsuka Europe and Otsuka UK submitted that it was taking this matter very seriously and it had been escalated to the Otsuka Europe Board. Details were provided.

Otsuka Europe and Otsuka UK concluded that it had not been possible to establish with certainty the reason for the omission. Certain key staff were no longer with the organisation and the recollection of events by those that remained were not consistent; poor meeting documentation had not assisted in this matter.

Otsuka Europe and Otsuka UK submitted that it was extremely disappointed to be in this position and sincerely apologised. Given Otsuka Europe's issues over the last 3 years in relation to similar matters and the focus that, as an organisation, it had had on addressing them, it considered that the omission of such key information from the prescribing information, and this omission not being picked up by either Otsuka Europe or Otsuka UK during the approval of the prescribing information, amounted to a failure to maintain high standards

Otsuka Europe and Otsuka UK also considered that the matters in this case were similar to those in Cases AUTH/3041/6/18 and AUTH/3042/6/18 and thus the omission in question amounted to a breach of the undertaking provided in these previous cases.

Overall, and given the repeated nature of this issue, Otsuka Europe and Otsuka UK considered that the matter had brought discredit upon, and reduced confidence in, the pharmaceutical industry, in breach of Clause 2.

The detailed response from Otsuka Europe and Otsuka UK is given below.

The Panel noted that the prescribing information with the omission was approved on 30 October 2020 by Otsuka Europe and 9 November 2020 by Otsuka UK and was subsequently used by both until 20 August 2021 and 25 August 2021 respectively.

Contrary to the relevant standard operating procedure (SOP), the Prescribing Information Review Committee did not meet until after the EC final decision, on 28 and 29 October to agree a draft revised version of the prescribing information. The Panel noted the companies' submissions about the meetings of the Prescribing Information Review Committee and their governance supported by the signed statements of attendees. It appeared that certain relevant text had been removed and inserted in a different section of the prescribing information but the frequency, 'monthly', was omitted from each/both section. The Prescribing Information Review Committee attendees' accounts differed about whether the omission of this term was discussed and the minutes were entirely silent on this point. The final track changed version of the prescribing information, agreed by the Prescribing Information Review Committee, showed that the sentence 'Administer once monthly as a single injection (no sooner than 26 days after the previous injection)' was deleted from the Prolonged-release suspension for injection subsection of the Dosage section. Some relevant text was moved to following the two injection start subsection of the Dosage section and read 'After either the one or the two injection start, the recommended maintenance dose of Abilify Maintena is 400mg (no sooner than 26 days after the previous injection). Consider reducing the dose to 300 mg once monthly if adverse reactions experienced' and this latter statement appeared in the prescribing information subsequently approved by Otsuka UK and Otsuka Europe.

The Panel noted the investigation report indicated that subsequent opportunities to identify the omission of 'monthly' from the prescribing information were missed. The omission was apparently first noted on 11 and 12 August 2021 at Otsuka Europe when a QC checker was reviewing relevant materials.

The Panel noted Otsuka's detailed submission about the withdrawal of the prescribing information from Otsuka Europe and the affiliates.

The Panel was concerned about what appeared to be serious failures on the part of both Otsuka UK and Otsuka Europe. This was of particular concern given that, as acknowledged in the voluntary admission, the companies had previously had difficulties with prescribing information and therefore, in the view of the Panel, should be paying particular attention to compliance in this area.

The Panel noted the multiple failures that led to the omission of the term 'monthly' in the prescribing information including the failure to comply with the SOP, poor governance at the Prescribing Information Review Committee, and the repeated failure to identify the omission when the relevant prescribing information was uploaded to PromoMats and approved at Otsuka Europe and Otsuka UK. It appeared, according to the Recall, Suspension, Withdrawal form, that the prescribing information at issue was included in seven Otsuka UK digital materials at the time of withdrawal and it was thus unclear why the error had not previously been noted either at certification or QC check stage of these materials. The Panel did not know whether the prescribing information in question had appeared in one-off use items that were no longer on the current materials list at the time the withdrawal took place. In the Panel's view, each company had failed to maintain high standards in this regard and a breach of the Code was ruled in relation to each company (Cases AUTH/3565/10/21 and AUTH/3566/10/21) as acknowledged by both companies.

It was crucial that health professionals and others could rely completely upon the industry for up-to-date and accurate information about their medicines particularly the

omission of which could potentially impact patient safety such as the omission of the maintenance dose from the prescribing information in question. The Panel noted the breadth and nature of the errors by each company set out above and the time the incorrect prescribing information was in use without the error being identified. The Panel considered that such failures brought discredit upon, and reduced confidence in, the pharmaceutical industry, a breach of Clause 2 was ruled in relation to each company (Cases AUTH/3565/10/21 and AUTH/3566/10/21), as acknowledged by both companies.

The Panel noted that the companies had provided separate undertakings in Cases AUTH/3041/6/18 and AUTH/3042/6/18 and compliance with each would be considered separately. The Panel noted that a form of undertaking and assurance was an important document which underpinned self-regulation. Companies had to give an undertaking that the material in question and any similar material, if not already discontinued or no longer in use would cease forthwith and give an assurance that all possible steps would be taken to avoid similar breaches of the Code in future (Paragraph 7.1 of the Constitution and Procedure). It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that the previous cases, Cases AUTH/3041/6/18 and AUTH/3042/6/18 concerned the companies' procedures for updating the summary of product characteristics (SPC) and prescribing information.

The Panel considered that the subject matter of Case AUTH/3042/6/18 was closely similar to the present case, Case AUTH/3566/10/21, and considered that Otsuka UK had failed to comply with its undertaking given in Case AUTH/3042/6/18. A breach of the Code was ruled as acknowledged by the company (Case AUTH/3566/10/21). The Panel noted the importance of complying with undertakings as set out above and in particular noted the imposition of audits further to Case AUTH/3042/6/18 was such that particular attention ought to have been paid to compliance and updating prescribing information. The Panel considered that Otsuka UK had reduced confidence in, and brought discredit upon, the pharmaceutical industry. A breach of Clause 2 was ruled as acknowledged by Otsuka UK (Case AUTH/3566/10/21).

The Panel considered that the subject matter of Case AUTH/3041/6/18 was closely similar to the present case, Case AUTH/3565/10/21, in this regard. Further, in Case AUTH/3041/6/18, the Panel had noted that the governance of materials at Otsuka Europe had fallen below acceptable standards and that good governance of the process for notifying affiliates of SPC and PIL updates was critical and had potential patient safety implications. In the present case, Case AUTH/3565/10/21, the Panel considered that, in general, and noting its comments and rulings above, Otsuka Europe's overall governance in relation to its processes for updating prescribing information, further to an SPC update, appeared to be poor and the subject matter of the voluntary admission was thereby also closely similar to the previous case, Case AUTH 3041/8/18, in this regard. The Panel, noting its comments and rulings above, considered that Otsuka Europe had breached the undertaking given in Case AUTH/3041/8/18 and a breach of the Code was ruled as acknowledged by Otsuka Europe (Case AUTH/3565/10/21).The Panel noted the importance of complying with undertakings as set out above and, in particular, noted that the imposition of audits further to Case AUTH/3041/6/18 was such that particular attention ought to have paid to compliance and updating prescribing information. The Panel considered that Otsuka Europe had reduced confidence in, and

brought discredit upon, the pharmaceutical industry. A breach of Clause 2 was ruled in relation to Otsuka Europe in Case AUTH/3565/10/21 as acknowledged by Otsuka Europe.

Otsuka Pharmaceutical Europe Limited (Case AUTH/3565/10/21) and Otsuka Pharmaceuticals (UK) Limited (Case AUTH/3566/10/21) submitted a joint voluntary admission in relation to the omission of the frequency of dosing for the intramuscular injection formulation from the prescribing information for Abilify/Abilify Maintena (aripiprazole) and in relation to a breach of undertaking.

COMPLAINT

Otsuka Europe and Otsuka UK considered that there might have been a breach of the Code in relation to the content of the prescribing information for Abilify (aripiprazole)/Abilify Maintena in that the prescribing information failed to refer to the frequency of dosing for the monthly intramuscular injection formulation. The prescribing information with this omission was approved and used by both Otsuka Europe and Otsuka UK therefore the voluntary admission was made jointly by both organisations.

Otsuka Europe and Otsuka UK submitted that it was taking this matter very seriously and it had been escalated to the Otsuka Europe Board. In terms of internal remediation, immediate action was taken to withdraw the prescribing information from the affiliates and to withdrawal any impacted material in the UK.

Background

Otsuka Europe and Otsuka UK submitted that the relevant European standard operating procedure (SOP) to communicate updates to summaries of product characteristics (SPC) and prescribing information was EU-SOP-MA-002 which required that, should a SPC revision result in the need to amend the relevant prescribing information, Otsuka Europe draft and approve this revised prescribing information centrally and provided it to the affiliates for local adaption.

Identification of the issue

As part of Otsuka Europe's preparation for attending the European College of Neuropsychopharmacology (ECNP) congress, it was identified that the prescribing information for Abilify/Abilify Maintena omitted any reference to the frequency of dosing for the intramuscular injection monthly formulation. This was notified to the Otsuka Europe Ethics & Compliance department on Thursday, 12 August and was raised as an incident.

An Incident Response Team was formed and met on Monday, 16 August and it was agreed that the omission would require a withdrawal of the prescribing information from the affiliates, with an instruction that all impacted material should be recalled within five working days.

Internal Investigation

Otsuka Europe and Otsuka UK had conducted a thorough investigation into this incident and it seemed that the omission was introduced when the prescribing information was revised in October 2020. The full investigation details could be found in the Incident Report, associated Chronology of Events Source Documents and Interview Notes. It was important that all of these

documents were reviewed so that a full understanding of the circumstances of this incident were well comprehended, however, a summary was provided below:

- On 18 September 2020 notification was received by Otsuka Europe from Global Regulatory Affairs Region Europe (GRA RE) of the agreement of the English language version of the Abilify Maintena SPC for the addition of a two injection start method of initiation:
    - According to the relevant SOP, the Prescribing Information Review Committee (PIRC) should have then met in order to agree a draft revised version of the Abilify/Abilify Maintena prescribing information.
    - However, it seemed that the PIRC did not meet until after the revised SPC was approved by the European Commission (EC).

- On 27 October 2020, GRA RE notified Otsuka Europe of the approval of the revised SPC by the EC.

- On 28 October 2020 the PIRC met to discuss the revised prescribing information. Following the meeting further revisions were made to the prescribing information by a member of the PIRC, including removal of 'monthly' in relation to the intramuscular injection formulation of Abilify Maintena:
    - Some of the text removed was added to a different section of the prescribing information, but 'monthly' was not.

- A second PIRC meeting took place on 29 October 2020:
    - The minutes for both meetings made no reference to the removal of 'monthly' from the prescribing information or included any indication that this was discussed during either meeting.

- The revised prescribing information was uploaded into the Otsuka Europe Document Approval System (PromoMats) on 30 October 2020 and approved on the same day:
    - The omission of 'monthly' was not identified.
    - Following approval the prescribing information was provided to the affiliates, including Otsuka UK, on the same day via the Regulatory electronic document management system. (CREDO)

- The revised prescribing information was approved by Otsuka UK on 9 November 2020:
    - The omission of 'monthly' was not identified.

Conclusion

Otsuka Europe and Otsuka UK submitted that it had not been possible to establish with certainty the reason why this omission was introduced into the prescribing information in October – November 2020. Certain key staff were no longer with the organisation and the recollection of events by those that remained were not consistent; poor meeting documentation had not assisted in this matter.

Otsuka Europe and Otsuka UK submitted that it was extremely disappointed to be in this position and sincerely apologised. Given Otsuka Europe's issues over the last 3 years in relation to similar matters and the focus that, as an organisation, it had had on addressing them,

it considered that the omission of such key information from the prescribing information, and this omission not being picked up by either Otsuka Europe or Otsuka UK during the approval of the prescribing information, amounted to a failure to maintain high standards by both Otsuka Europe and Otsuka UK, in breach of Clause 9.1 (the 2019 Code would apply given that the issue arose in October 2020).

Otsuka Europe and Otsuka UK also considered that the matters in this case were similar to those in Cases AUTH/3041/6/18 and AUTH/3042/6/18 in that both Otsuka Europe and Otsuka UK used prescribing information that was not consistent with the Abilify Maintena SPC, amounting to a breach of the undertaking provided in these previous cases, in breach of Clause 29 (2019 Code).

Overall, and given the repeated nature of this issue, Otsuka Europe and Otsuka UK considered that the matter had brought discredit upon, and reduced confidence in, the pharmaceutical industry, in breach of Clause 2. Internal remediation and action had already been taken.

Otsuka was asked to respond in relation to Clauses 2, 9.1 and 29 of the 2019 Code.

RESPONSE

Otsuka Europe and Otsuka UK confirmed that it had no further comment in relation to the requirements of Clauses 2, 9.1 and 29 of the 2019 Code.

Otsuka Europe and Otsuka UK confirmed that the recall of the prescribing information in Otsuka Europe was completed on 20 August 2021.

The companies submitted that the delay in withdrawing the prescribing information in the Otsuka Pharmaceuticals (UK) Ltd approval system had no impact on ensuring materials were withdrawn from use. The recall of materials from Otsuka UK staff was completed on 25 August 2021 as was the recall of the prescribing information to which digital material linked.

PANEL RULING

The Panel noted the voluntary admission concerned, *inter alia*, the omission of the frequency of maintenance dosing for the intramuscular injection formulation from the prescribing information for Abilify/Abilify Maintena further to an SPC update introducing a two start dosing initiation. The prescribing information with the omission was approved on 30 October 2020 by Otsuka Europe and 9 November 2020 by Otsuka UK and was subsequently used by both until 20 August 2021 and 25 August 2021 respectively.

The Panel noted that the companies had submitted a joint admission and joint response. The Panel noted the close collaboration between the companies on certain aspects of the subject matter of the voluntary admission including that the Prescribing Information Review Committee had to include a UK employee from medical if the product in question was marketed in the UK and that it appeared from the Prescribing Review Committee minutes dated 28 and 29 October 2020 that the meetings in question, whilst chaired by medical affairs Europe, were attended by one member of UK medical.

The Panel noted that the positive opinion of the Committee for Medicinal Products for Human Use (CHMP) for the Type II variation for Abilify Maintena was received on 18 September 2020

and the European Commission (EC) final approval was received on 27 October 2020. Section 4.2, Posology and method of administration, of the updated SPC for Abilify Maintena, after detailing the two starting dose regimens (one injection and two injection start), stated that after the injection start the recommended maintenance dose of Abilify Maintena was 400mg and that it 'should be administered once monthly as a single injection (no sooner than 26 days after the previous injection)'.

Contrary to the relevant SOP 'EU-SOP-MA-002 Notification by OPEL/OPNL of Changes to SmPC, PL and PI to the OPEL affiliates', the Prescribing Information Review Committee did not meet until after the EC final decision, on 28 and 29 October to agree a draft revised version of the prescribing information. The Panel noted the companies' submissions about the meetings of the Prescribing Information Review Committee and their governance supported by the signed statements of attendees. It appeared that certain relevant text had been removed and inserted in a different section of the prescribing information but the frequency, 'monthly', was omitted from either section. The Prescribing Information Review Committee attendees' accounts differed about whether the omission of this term was discussed and the minutes were entirely silent on this point. The final track changed version of the prescribing information, agreed by the Prescribing Information Review Committee, showed that the sentence 'Administer once monthly as a single injection (no sooner than 26 days after the previous injection)' was deleted from the Prolonged-release suspension for injection subsection of the Dosage section. Some relevant text was moved to following the two injection start subsection of the Dosage section and read 'After either the one or the two injection start, the recommended maintenance dose of Abilify Maintena is 400mg (no sooner than 26 days after the previous injection). Consider reducing the dose to 300 mg once monthly if adverse reactions experienced' and this latter statement appeared in the prescribing information subsequently approved by Otsuka UK and Otsuka Europe.

The Panel noted the investigation report indicated that subsequent opportunities to identify the omission of 'monthly' from the prescribing information were missed including when the revised prescribing information was approved at Otsuka Europe (30 October 2020) and by Otsuka UK (9 November 2020). The omission was apparently first noted on 11 and 12 August 2021 at Otsuka Europe when a QC checker was reviewing materials which included the prescribing information for Abilify/Abilify Maintena to be used by Otsuka Europe at a conference.

The Panel noted Otsuka's submission that an Incident Response Team was formed and met on Monday, 16 August 2021 when it was agreed that the omission would require a withdrawal of the prescribing information from Otsuka Europe and the affiliates, with an instruction that all impacted material should be recalled within five working days. The chronology indicated that the prescribing information recall from affiliates was initiated on 19 August and withdrawn in Otsuka Europe PromoMats that day. The prescribing information recall was completed at Otsuka UK on 25 August and withdrawn from UK PromMats on 16 September. The reason given for the delayed withdrawal from UK PromoMats was that it was 'due to an oversight'. The Panel noted Otsuka's submission that the delay in withdrawing the prescribing information in the Otsuka UK approval system had no impact on ensuring materials were withdrawn from use, the recall of materials from staff was completed on 25 August 2021 as was the recall of the prescribing information to which the digital materials linked.

The Panel was concerned about what appeared to be serious failures on the part of both Otsuka UK and Otsuka Europe. This was of particular concern given that, as acknowledged in the voluntary admission, the companies had previously had difficulties with prescribing

information and therefore, in the view of the Panel, should be paying particular attention to compliance in this area.

The Panel noted the multiple failures that led to the omission of the term 'monthly' in the prescribing information including the failure to comply with the SOP, poor governance at the Prescribing Information Review Committee, and the repeated failure to identify the omission when the relevant prescribing information was uploaded to PromoMats and approved at Otsuka Europe and Otsuka UK. It appeared that the prescribing information at issue was included in seven Otsuka UK digital materials at the time of withdrawal and it was thus unclear why the error had not previously been noted either at certification or QC check stage of these materials. The Panel did not know whether the prescribing information in question had appeared in one-off use items that were no longer on the current materials list at the time the withdrawal took place. In the Panel's view, each company had failed to maintain high standards in this regard and a breach of Clause 9.1 was ruled in relation to each company (Cases AUTH/3565/10/21 and AUTH/3566/10/21) as acknowledged by both companies.

It was crucial that health professionals and others could rely completely upon the industry for up-to-date and accurate information about their medicines particularly the omission of which could potentially impact patient safety such as the omission of the maintenance dose from the prescribing information in question. The Panel noted the breadth and nature of the errors by each company set out above and the time the incorrect prescribing information was in use without the error being identified. The Panel considered that such failures brought discredit upon, and reduced confidence in, the pharmaceutical industry, a breach of Clause 2 was ruled in relation to each company (Cases AUTH/3565/10/21 and AUTH/3566/10/21), as acknowledged by both companies.

The Panel noted the companies' admission that they considered that the matters in this case were similar to those in Cases AUTH/3041/6/18 and AUTH/3042/6/18 in that both Otsuka Europe and Otsuka UK used prescribing information that was not consistent with the Abilify Maintena SPC, amounting to a breach of the undertaking provided in these previous cases, in breach of Clause 29 (2019 Code).

The Panel noted that the companies had provided separate undertakings in Cases AUTH/3041/6/18 and AUTH/3042/6/18 and compliance with each would be considered separately. The Panel noted that a form of undertaking and assurance was an important document which underpinned self-regulation. Companies had to give an undertaking that the material in question and any similar material, if not already discontinued or no longer in use would cease forthwith and give an assurance that all possible steps would be taken to avoid similar breaches of the Code in future (Paragraph 7.1 of the Constitution and Procedure). It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted that the previous cases, Cases AUTH/3041/6/18 and AUTH/3042/6/18 concerned the companies' procedures for updating the summaries of product characteristics (SPC) and prescribing information.

The Panel noted that Case AUTH/3042/6/18, which concerned Otsuka UK, multiple rulings of breaches of the Code were ruled including in relation to Jinarc promotional materials and five Abilify Maintena materials that did not contain the latest version of prescribing information as it was inconsistent with the SPC current at that time and one Abilify Maintena item that omitted prescribing information. The Panel considered that the subject matter of Case AUTH/3042/6/18

was closely similar to the present case, Case AUTH/3566/10/21, and considered that Otsuka UK had failed to comply with its undertaking given in Case AUTH/3042/6/18. A breach of Clause 29 was ruled as acknowledged by the company (Case AUTH/3566/10/21). The Panel noted the importance of complying with undertakings as set out above and in particular noted the imposition of audits further to Case AUTH/3042/6/18 was such that particular attention ought to have been paid to compliance and updating prescribing information. The Panel considered that Otsuka UK had reduced confidence in, and brought discredit upon, the pharmaceutical industry. A breach of Clause 2 was ruled as acknowledged by Otsuka UK (Case AUTH/3566/10/21).

The Panel noted that in Case AUTH/3041/6/18, which concerned Otsuka Europe, rulings of breaches of the Code were ruled in relation to Jinarc promotional materials issued by Otsuka Europe that did not contain the latest version of the prescribing information and two Abilify Maintena materials that were missing prescribing information. The Panel considered that the subject matter of Case AUTH/3041/6/18 was closely similar to the present case, Case AUTH/3565/10/21, in this regard. Further, in Case AUTH/3041/6/18, the Panel had noted that the governance of materials at Otsuka Europe had fallen below acceptable standards and that good governance of the process for notifying affiliates of SPC and PIL updates was critical and had potential patient safety implications. In the present case, Case AUTH/3565/10/21, the Panel considered that, in general, and noting its comments and rulings above, Otsuka Europe's overall governance in relation to its processes for updating prescribing information, further to an SPC update, appeared to be poor and the subject matter of the voluntary admission was thereby also closely similar to the previous case, Case AUTH 3041/8/18, in this regard. The Panel, noting its comments and rulings above, considered that Otsuka Europe had breached the undertaking given in Case AUTH/3041/8/18 and a breach of Clause 29 was ruled as acknowledged by Otsuka Europe (Case AUTH/3565/10/21).

The Panel noted the importance of complying with undertakings as set out above and, in particular, noted that the imposition of audits further to Case AUTH/3041/6/18 was such that particular attention ought to have paid to compliance and updating prescribing information. The Panel considered that Otsuka Europe had reduced confidence in, and brought discredit upon, the pharmaceutical industry. A breach of Clause 2 was ruled in relation to Otsuka Europe in Case AUTH/3565/10/21 as acknowledged by Otsuka Europe.

The Panel was extremely concerned that a breach of undertaking occurred in relation to each company. The Panel, however, considered that, on balance, and bearing in mind the need for proportionate regulation, it would not report Otsuka Europe and Otsuka UK to the Appeal Board under Paragraph 8.2 of the Constitution and Procedure for these current cases as closely similar matters had been at issue in Cases AUTH/3041/6/18 and AUTH/3042/6/18 which had led to the audit process which was ongoing when the Panel considered this matter. The Panel further bore in mind that the Appeal Board received all cases completed at the Panel level and therefore the Appeal Board could, at that point, consider if additional sanctions might be appropriate in relation to Cases AUTH/3565/10/21 and AUTH/3566/10/21.

Complaint received **1 October 2021**

Case completed **16 February 2022**