CASE AUTH/3489/3/21

VOLUNTARY ADMISSION BY OTSUKA EUROPE

Communication of revision of Samsca summary of product characteristics

Otsuka Pharmaceutical Europe made a voluntary admission in relation to the notification to Otsuka Europe affiliates of a recent update to the summary of product characteristics (SPC) and prescribing information for Samsca (tolvaptan).

Samsca was indicated in adults for the treatment of hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

As Paragraph 5.6 of the Constitution and Procedure required the Director to treat a voluntary admission as a complaint, the matter was taken up with Otsuka Europe.

Otsuka Europe stated that it took the matter very seriously and it had been escalated to and discussed at both the Otsuka Europe Audit, Risk & Compliance Committee and the Otsuka Europe Board of Directors. In terms of internal remediation, action had already been taken.

Otsuka Europe provided copies of the previous version of the Samsca SPC, the revised Samsca SPC and the prescribing information effective when the SPC revision was approved. The company also provided a copy of the relevant European standard operating procedure (SOP) (ref EU-SOP-MA-002) and its timelines for communication of an SPC revision.

The recent Samsca SPC revision had been anticipated for some months and details were provided including that receipt of the approval of the revision was anticipated on 4 January 2021.

Health authority approval was received by Global Regulatory Affairs Region Europe on 22 December and this was communicated to Otsuka Europe Medical Affairs on 28 December, within the timelines specified in the relevant SOP. The notification to the affiliates should then have been sent by the close of the business day on 4 January 2021 however, it was not sent out until 8 January 2021. In the meantime, two members of staff had formally raised concerns that the SOP timelines were not being adhered to. In addition, the wording in the prescribing information was impacted by the SPC revision but revised prescribing information was not provided to the affiliates until 18 January 2021.

Otsuka Europe submitted that it had conducted a thorough investigation and details were provided.

In conclusion, Otsuka Europe stated that it was not a process issue. Whilst Otsuka Europe would make some small revisions to the relevant SOP as a result of this, these were considered part of ongoing continuous quality improvement activities and they would not have prevented the incident at issue. It was clear that the SOP was not

followed by the senior medical member of staff. There were some mitigating circumstances, but there was a failure to plan for, or react to, these in the manner expected of a senior employee.

Otsuka Europe stated that it was extremely disappointed to be in this position and sincerely apologised, although it was encouraged that a number of employees raised concerns about the matter internally following its whistleblowing process. 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, the company considered that the failure to follow the relevant SOP in this instance amounted to a failure to maintain high standards.

Otsuka Europe stated that it also considered that the matters in this case were similar to those in Case AUTH/3041/6/18 in that Otsuka Europe did not promptly communicate with affiliates about the Samsca SPC update in accordance with the relevant SOP, in breach of the undertaking provided in that case.

Overall, and given the seniority of the individual involved, Otsuka Europe 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.

The response from Otsuka Europe is given below.

The Panel noted that Otsuka Europe's headquarters were based in the UK. Otsuka Europe was a member of the ABPI and thus obliged to comply with the Code. The Panel noted that Otsuka Europe was the marketing authorisation holder for Samsca which was supplied in the UK by Otsuka UK.

The Panel noted Otsuka Europe's submission that the timelines in the relevant SOP (EU-SOP-MA-002) for notification of affiliates of an SPC revision and for updating the associated prescribing information were not followed. The Panel noted Otsuka Europe's submission including following the receipt of health authority approval on 22 December. It further noted that the wording in the prescribing information was impacted by the SPC revision but revised prescribing information was not provided to the affiliates until 18 January 2021. The Panel noted Otsuka Europe's submission that on 6 January 2021 it was agreed between regulatory affairs and the senior medical member of staff that the prescribing information required revision but that the revision was minor and could wait until the next required revision. On 12 January 2021, however, as part of reviewing all documentation related to this matter, the incident response team reviewed the Samsca prescribing information and considered that a revision was required as a result of the SPC update and the senior leadership emailed the senior medical member of staff on 13 January 2021 stating that the Samsca prescribing information should be revised. On 14 January 2021 the revised prescribing information was approved by the prescribing information review committee. On 18 January 2021 the senior medical member of staff confirmed by email that the revised prescribing information had been approved in Otsuka Europe's document approval system and disseminated to the affiliates.

The Panel noted Otsuka Europe's submission that Samsca was not promoted in the UK therefore the delay in providing revised prescribing information to affiliates did not impact any activity falling within the scope of the Code and that the revised SPC was

published on the eMC on 13 January 2021 within the SOP timeline. Whilst Samsca was not promoted in the UK the Panel did not know given its UK availability whether there were any non-promotional materials that might be affected by an SPC update. Overall, the Panel considered that the delay in notifying affiliates of the updated SPC and prescribing information by a senior member of staff including the failure to ensure that the absence of a key member of staff did not impact compliance matters meant that Otsuka Europe had failed to maintain high standards and a breach of the Code was ruled as acknowledged by Otsuka Europe.

The Panel noted that in the previous case, Case AUTH/3041/16/18 there were instances where Otsuka UK had not received prompt communication from Otsuka Europe regarding an SPC update. The Panel in that case noted that good governance of the process for notifying affiliates of SPC and package information leaflet updates was critical and had potential patient safety implications and considered that, in general, Otsuka Europe's overall governance in relation to its processes and materials had fallen below acceptable standards. The Panel in that case considered that high standards had not been maintained and a breach of the Code was ruled.

Turning to the present case, Case AUTH/3489/3/21, the Panel noted its comments and rulings above and considered that its ruling of a breach of the Code for the failure to promptly notify the affiliates of the SPC change and to promptly provide the updated prescribing information each in accordance with the relevant SOP meant that it had breached the undertaking given in the previous case, Case AUTH/3041/16/18. The Panel therefore ruled a breach of the Code.

The Panel noted that it was reassuring that two members of staff had formally raised concerns that the SOP timelines were not being adhered to. Nonetheless, the Panel noted that good governance of the process for notifying affiliates of an SPC update and the provision of new prescribing information was critical and the Panel noted the seniority of at least one member of staff who had a relevant role in this matter. In the Panel's view, its concerns were compounded by the fact that at the relevant time the company was subject to the PMCPA auditing process about matters that were similar to the subject of the current voluntary admission and therefore compliance with procedures in relation to SPC updates and the provision of prescribing information ought to have been front of mind. The Panel considered that Otsuka Europe's breach of undertaking meant that it had brought discredit upon, and reduced confidence in, the pharmaceutical industry and a breach of Clause 2 was ruled.

Otsuka Pharmaceutical Europe Limited made a voluntary admission in relation to the notification to Otsuka Europe affiliates of a recent update to the summary of product characteristics (SPC) and prescribing information for Samsca (tolvaptan).

Samsca was indicated in adults for the treatment of hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

As Paragraph 5.6 of the Constitution and Procedure required the Director to treat a voluntary admission as a complaint, the matter was taken up with Otsuka Europe.

VOLUNTARY ADMISSION

Otsuka Europe stated that it took the matter very seriously and it had been escalated to and discussed at both the Otsuka Europe Audit, Risk & Compliance Committee and the Otsuka Europe Board of Directors. In terms of internal remediation, action had already been taken.

Otsuka Europe provided copies of the previous version of the Samsca SPC, the revised Samsca SPC and the prescribing information effective when the SPC revision was approved.

Otsuka Europe provided a copy of the relevant European standard operating procedure (SOP) (ref EU-SOP-MA-002) and noted that the current version used the Otsuka regulatory documents management system, CREDO, to notify affiliates of SPC and prescribing information revisions and the same system to track affiliates responses. This version became effective on 20 December 2019 and had been followed to communicate SPC revisions eight times prior to this revision without any process issues.

The timelines for communication of an SPC revision as set out in the SOP were as follows (OPEL refers to Otsuka Europe and PI refers to prescribing information):

Working day	Step required by the Relevant SOP
0	Receipt by Otsuka Global Regulatory Affairs Region Europe (GRA RE) of approved SmPC from a health authority
2	Communication by GRA RE of the revised SmPC to OPEL Medical Affairs
4	Notification via CREDO by OPEL Therapy Area (TA) Lead to affiliates of the SmPC revision (and PI revision if the PI was impacted)
5	Affiliates acknowledged in CREDO receipt of the notification and that the instructions provided would be followed
9	Completion of withdrawal of any impacted materials
14	Initiation of the update of any third-party websites with the revised SPC e.g., the Electronic Medicines Compendium (eMC) in the UK

In the case of the recent Samsca SPC revision, it had been anticipated for some months (copies provided of the minutes of the Regulatory Affairs/Medical Affairs (RAMA) meetings for September, October, November and December 2020, and associated RAMA Tracker) and a communication was sent by Global Regulatory Affairs Region Europe to Otsuka Europe Medical Affairs on 30 September 2020 indicating the revision wording. In the December RAMA meeting it was documented that receipt of the approval of the revision was anticipated on 4 January 2021.

Health authority approval was received by Global Regulatory Affairs Region Europe on 22 December and this was communicated to Otsuka Europe Medical Affairs on 28 December, within the timelines specified in the relevant SOP.

The notification to the affiliates should then have been sent to the affiliates by the close of the business day on 4 January 2021; however, it was not sent out until 8 January 2021. In the meantime, two members of staff had formally raised concerns that the SOP timelines were not being adhered to. In addition, the wording in the prescribing information was impacted by the

SPC revision but revised prescribing information was not provided to the affiliates until the 18 January 2021.

Otsuka Europe submitted that it had conducted a thorough investigation and provided a copy of the incident report, details of the 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, in summary:

- When the Samsca SPC was revised the position of therapeutic area lead for nephrology was vacant and the role was covered by a senior medical member of staff who was on annual leave (details provided). No deputy had been nominated during his/her period of absence.

- On 4 January 2021, Global Regulatory Affairs Region Europe sent a 'reminder' email follow up to that sent on 28 December indicating that the affiliates should be notified of the revision to the Samsca SPC, in accordance with the relevant SOP (copy provided).

- On 4 and 5 January 2021, two members of staff from Otsuka Europe medical affairs Europe and someone from regulatory affairs region Europe sent separate messages in various formats to the senior medical member of staff enquiring as to whether the notification to the affiliates was on track. The importance of the notification was said to be emphasised and assistance offered if required.

- On 5 January 2021 the senior medical member of staff replied to one of the messages referred to above and stated that the notification was not on track and that 'the team' should get together 'urgently'. Other information was provided including that the senior medical member of staff claimed to have issues accessing CREDO but that there was no evidence that he/she had reached out for support to complete the necessary action or assist with access to CREDO. At an *ad hoc* Otsuka Europe senior leadership team meeting on 5 January it was not made clear that the timeline in the SOP for communicating an SPC revision to the affiliates had not been met or that the senior medical member of staff had issues sending out a communication.

- On 6 January 2021 an employee from regulatory affairs region Europe and the senior medical member of staff discussed the matter and agreed that the prescribing information required revision but that the revision was minor and could wait until the next required revision of the prescribing information. Further details were provided including that the senior medical member of staff understood from the wording in the relevant SOP that minor amendments required to prescribing information that did not impact on prescribing habits could be delayed until the next required revision.

- On 7 January concerns were raised internally as noted above.

- On 8 January, a meeting was held to discuss the concerns raised, attended by Otsuka Europe senior leadership, compliance, and legal staff.

- It was agreed at the meeting that Otsuka Europe senior leadership should contact the senior medical member of staff in order to get an update on progress of notifying the

affiliates of the SPC revision. The Otsuka Europe senior leadership was informed that the notification would go out later that day and that no change to the prescribing information was required.

- On 8 January 2021 the senior medical member of staff accessed CREDO and realised that he/she did not have the appropriate rights in the system in order to initiate the notification to the affiliates; he/she then contacted a member of the regulatory affairs Europe team for assistance and the notification was sent out to the affiliates that evening.

- On 12 January 2021, as part of reviewing all documentation related to this matter, the incident response team reviewed the Samsca prescribing information and considered that a revision was required as a result of the SPC revision:

    - Samsca was not promoted in the UK therefore the delay in providing revised prescribing information to affiliates did not impact on any activity falling within the scope of the Code.

- On 13 January 2021 Otsuka Europe senior leadership emailed the senior medical member of staff stating that Samsca prescribing information should be revised.

- On 14 January 2021 the revised prescribing information was approved by the prescribing information review committee.

- On 15 January 2021, following a discussion with ethics and compliance, senior medical member of staff instructed the affiliates via email to expedite the initiation of the update of external websites with the revised SPC in order for the SOP timelines to be met:

    - The update of the electronic medicines compendium (eMC) with the revised Samsca SPC was initiated on 11 January 2021 and the revised SPC was published in the eMC on 13 January 2021. Thus the timelines to update the eMC stated in the SOP were met by Otsuka UK.

- On 18 January 2021 the senior medical member of staff confirmed on email that the revised prescribing information had been approved in Otsuka Europe's document approval system and disseminated to the affiliates.

Otsuka noted that its IT records showed that there were no access issues with the relevant IT (5 – 7 January 2021) or activity log for the senior medical member of staff (4 – 7 January 2021).

In conclusion, Otsuka Europe stated that it was not a process issue. Whilst Otsuka Europe would make some small revisions to the relevant SOP as a result of this, these were considered part of ongoing continuous quality improvement activities and they would not have prevented the incident at issue. It was clear that the SOP was not followed by the senior medical member of staff. There were some mitigating circumstances (details provided), but there was a failure to plan for, or react to, these in the manner expected of a member of the senior leadership team.

Otsuka Europe stated that it was extremely disappointed to be in this position and sincerely apologised, although it was encouraged that a number of employees raised concerns about the

matter internally following its whistleblowing process. 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, the company considered that the failure to follow the relevant SOP in this instance amounted to a failure to maintain high standards, in breach of Clause 9.1.

Otsuka Europe stated that it also considered that the matters in this case were similar to those in Case AUTH/3041/6/18 in that Otsuka Europe did not promptly communicate with affiliates about the Samsca SPC update in accordance with the relevant SOP, in breach of the undertaking provided in that case and thus in breach of Clause 29.

Overall, and given the seniority of the individual involved, Otsuka Europe 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.

During the investigation of this matter a concern was raised that a separate communication to affiliates on 4 February 2021 about an anticipated revision to the Jinarc SPC might have caused confusion. This was also investigated and it was concluded that, whilst the communication used a template that should have been used later in the process described in the relevant SOP, and thus there were some inaccuracies in the communication, there was no evidence that the email of 4 February 2021 confused the recipients. There was, however, evidence that the working practice associated with the relevant SOP (ref MA-002-WP-EU-01 v1.0) was not followed in that the prescribing information review committee did not review the full draft prescribing information vs the entire agreed English version of the SPC. Otsuka Europe stated that it had identified a number of corrective and preventive actions to address that.

Whilst Otsuka Europe did not consider that this second incident warranted a voluntary admission to the PMCPA, given the similarities to the first incident it had included investigational documentation in the interests of transparency.

When writing to Otsuka, the Authority asked it to consider the requirements of Clauses 29, 9.1 and 2 of the Code.

RESPONSE

Otsuka Europe stated that it had no further comments in relation to the requirements of Clauses 29, 9.1 and 2 of the Code.

Otsuka Europe noted the question as to why some members of staff decided that materials did not need to be updated in relation to the change from 'lapp lactase deficiency' to 'total lactase deficiency' in section 4.4 of the Samsca SPC. This was addressed in the interviews with staff.

Specifically, the regulatory affairs region Europe employee stated:

> '.. this change was just a minor semantic one and we agreed that the prescribing information revision could wait until the next time it needed to be revised.'

The senior medical member of staff stated:

'I discussed this with [regulatory affairs Europe] and we agreed that this was a minor change. There was a lot of work involved in the update of prescribing information so we agree that this could wait until the next revision of the prescribing information.'

'We decided that this was a minor linguistic change that would not impact on how the medicine was prescribed so the revision could wait until the next revision of the prescribing information.'

PANEL RULING

The Panel noted that Otsuka Europe's headquarters were based in the UK. Otsuka Europe was a member of the ABPI and thus obliged to comply with the Code. The Panel noted that Otsuka Europe was the marketing authorisation holder for Samsca which was supplied in the UK by Otsuka UK.

The Panel noted Otsuka Europe's submission that the timelines in the relevant SOP (EU-SOP-MA-002) for notification of affiliates of an SPC revision and for updating the associated prescribing information were not followed. The Panel noted Otsuka Europe's submission that the Samsca SPC revision in question had been anticipated for some months. Health authority approval was received by Global Regulatory Affairs Region Europe on 22 December 2020 and was communicated to Otsuka Europe Medical Affairs within the timelines specified in the relevant SOP on 28 December. The Panel further noted Otsuka Europe's submission that whilst the notification should have been sent to the affiliates by the close of the business day on 4 January 2021, it was not sent out until 8 January 2021. In addition, the wording in the prescribing information was impacted by the SPC revision but revised prescribing information was not provided to the affiliates until 18 January 2021. The Panel noted Otsuka Europe's submission that on 6 January 2021 it was agreed between an employee of regulatory affairs region Europe and the senior medical member of staff that the prescribing information required revision but that the revision was minor and could wait until the next required revision. On 12 January 2021, however, as part of reviewing all documentation related to this matter, the incident response team reviewed the Samsca prescribing information and considered that a revision was required as a result of the SPC update and Otsuka Europe senior leadership emailed the senior medical member of staff on 13 January 2021 stating that the Samsca prescribing information should be revised. On 14 January 2021 the revised prescribing information was approved by the prescribing information review committee. On 18 January 2021 the senior medical member of staff confirmed by email that the revised prescribing information had been approved in Otsuka Europe's document approval system and disseminated to the affiliates.

The Panel noted Otsuka Europe's submission that Samsca was not promoted in the UK therefore the delay in providing revised prescribing information to affiliates did not impact any activity falling within the scope of the Code and that the revised SPC was published on the eMC on 13 January 2021 within the SOP timeline. Whilst Samsca was not promoted in the UK the Panel did not know given its UK availability whether there were any non-promotional materials that might be affected by an SPC update. Overall, the Panel considered that the delay in notifying affiliates of the updated SPC and prescribing information by a senior member of staff including the failure to ensure that the absence of a key member of staff did not impact compliance matters meant that Otsuka Europe had failed to maintain high standards and a breach of Clause 9.1 was ruled as acknowledged by Otsuka Europe.

The Panel noted that in the previous case, Case AUTH/3041/16/18 there were instances where Otsuka UK had not received prompt communication from Otsuka Europe regarding an SPC update. The Panel in that case noted that good governance of the process for notifying affiliates of SPC and PIL updates was critical and had potential patient safety implications and considered that, in general, Otsuka Europe's overall governance in relation to its processes and materials had fallen below acceptable standards. The Panel in that case considered that high standards had not been maintained and a breach of Clause 9.1 was ruled.

Turning to the present case, Case AUTH/3489/3/21, the Panel noted its comments and rulings above and considered that its ruling of a breach of Clause 9.1 for the failure to promptly notify the affiliates of the SPC change and to promptly provide the updated prescribing information each in accordance with the relevant SOP meant that it had breached the undertaking given in the previous case, Case AUTH/3041/16/18. The Panel therefore ruled a breach of Clause 29.

The Panel noted that it was reassuring that two members of staff had formally raised concerns that the SOP timelines were not being adhered to. Nonetheless, the Panel noted that good governance of the process for notifying affiliates of an SPC update and the provision of new prescribing information was critical and the Panel noted the seniority of at least one member of staff who had a relevant role in this matter. In the Panel's view, its concerns were compounded by the fact that at the relevant time the company was subject to the PMCPA auditing process about matters that were similar to the subject of the current voluntary admission and therefore compliance with procedures in relation to SPC updates and the provision of prescribing information ought to have been front of mind. The Panel considered that Otsuka Europe's breach of undertaking meant that it had brought discredit upon, and reduced confidence in, the pharmaceutical industry and a breach of Clause 2 was ruled.

* * * * *

During its consideration of this case, the Panel noted the comments Otsuka had made in relation to Jinarc and an anticipated revision to the Jinarc SPC which might have caused confusion. There was, however, evidence that the working practice associated with the relevant SOP (ref MA-002-WP-EU-01 v1.0) was not followed in that the prescribing information review committee did not review the full draft prescribing information vs the entire agreed English version of the SPC. Otsuka Europe stated that it had identified a number of corrective and preventive actions to address that. The Panel noted with concern that this appeared to be another example of senior staff not following the relevant procedures and asked that Otsuka be advised of its views in this regard.

* * * * *

Complaint received **10 March 2021**

Case completed **4 January 2022**