CASE AUTH/3169/3/19

VOLUNTARY ADMISSION FROM OTSUKA EUROPE

Revision of Jinarc SPC

Otsuka Pharmaceuticals Europe, voluntarily admitted that it might have breached the Code with regard to updates to the Jinarc (tolvaptan) summary of product characteristics (SPC). Jinarc was used in certain patients with chronic kidney disease.

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 explained that there had been two parallel revisions to the Jinarc SPC since November and these had been communicated to the marketing authorization holder and all relevant European affiliates. The preliminary investigation concluded that communication to the affiliates on 14 February could have been clearer on this point.

Otsuka Europe regretted that communications to EU affiliates about SPC revisions had caused confusion and that as a result there was a Jinarc SPC available on the eMC from 15 February to 1 March which contained the latest revision (addition of gout) but not the preceding revision (addition of blister wallet cards). Otsuka Europe was concerned that there might have been a breach of the undertakings given in Cases AUTH/3041/6/18 and AUTH/3123/11/18.

Otsuka Europe stated that it also became aware in January 2019 that there was a mistake in the packaging and release of the Jinarc package leaflet in that the previous version of the package leaflet was packaged with the product. The company notified the EMA and the Medicines and Healthcare products Regulatory Agency (MHRA) on 17 January 2019 about that situation. During the following days the issue was discussed with the EMA. The EMA confirmed on 6 February that no Direct Healthcare Professional Communication (DHPC) was required.

The detailed response from Otsuka Europe is given below.

The Panel noted that there had been two parallel revisions to the Jinarc SPC (addition of blister in wallets cards with new marketing authorization numbers and addition of gout as a common adverse drug reaction) and that the two revisions were each subject to separate applications to the EMA and therefore a combined consolidated version also had to be approved by the EMA.

The Panel noted, based on Otsuka Europe's submission, that when two or more variation applications were submitted and/or assessed in parallel by the EMA, the procedures were kept separate, and further noted Otsuka Europe's submission that, in this case, having an SPC with gout but without the preceding blister wallet cards revision was unavoidable. However, the Panel noted Otsuka Europe's submission that the communication to the affiliates dated 14 February regarding this matter could have been clearer so they could have planned how to deal with this situation, and that the communication regarding the consolidated SPC sent to the affiliates on 26 February had not followed the relevant SOP and caused confusion in the affiliates.

The Panel considered that the lack of clear communication by Otsuka Europe to its affiliates, which was compounded by the failure to follow, and lack of consistent application of, the relevant SOP, meant that Otsuka Europe had failed to maintain high standards and a breach was ruled.

The Panel noted that in Case AUTH/3041/6/18, Otsuka Europe was found in breach of the Code for promotional materials either missing prescribing information or not containing the latest version of the prescribing information, for Otsuka Europe's governance of materials falling below acceptable standards, and Clause 2 for, *inter alia*, not providing prompt communication to Otsuka UK regarding SPC updates and poor governance which the Panel had considered had potential safety implications. Although there was some overlap between Case AUTH/3041/6/18 and the current case, the Panel noted that there were important differences. The subject matter of the former did not include the accuracy of communications about SPC updates in relation to Jinarc. The voluntary admission in Case AUTH/3169/3/19 did not refer to use of materials with the incorrect prescribing information. The Panel therefore considered, on balance, that the subject matter of the current case was sufficiently different to Case AUTH/3041/6/18 such that there was no breach of the undertaking given in that case. The Panel therefore ruled no breach of the Code including Clause 2 in this regard.

In relation to the admission of a breach of undertaking and Case AUTH/3123/11/18, Otsuka Europe referred to the email from Global Regulatory Affairs Region Europe dated 26 February 2019 and failure to follow process and causing confusion. In Case AUTH/3123/11/18, Otsuka Europe was found in breach of, *inter alia*, Clause 9.1 for lack of clear and consistent instructions to employees and third parties in relation to SPC changes and Clause 2 for its failure to timely and robustly address inadequacies in this process. The Panel considered that the breach of Clause 9.1 for the lack of clear communication to its affiliates and lack of consistent application of the relevant SOP in the current case (Case AUTH/3169/3/19) meant that Otsuka Europe had breached the undertaking given in Case AUTH/3123/11/18. The Panel therefore ruled a breach of Clause 29. 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.

The Panel noted Otsuka Europe's admission in relation to an out-of-date package leaflet being packaged with Jinarc at the manufacturing site. The Panel noted Otsuka Europe's submission that the manufacturing site was notified on 12 October 2018 of an upcoming revision to the leaflet with an implementation of 30 November 2018 but it mistakenly used the previous version. The Panel considered that Otsuka Europe had been let down by its manufacturing site. The Panel considered that the package leaflet was an important document for patients and such an error meant that Otsuka Europe had failed to maintain high standards and a breach of the Code was ruled. The Panel considered that a breach of Clause 2 was a sign of particular censure. The Panel noted that Otsuka Europe had liaised with the European Medicines Agency (EMA) and the Medicines and Healthcare Products Regulatory Agency (MHRA) with regard to this error and noted the actions Otsuka Europe submitted that it had agreed with the EMA on the matter. The Panel considered that, in these particular circumstances, and on balance, no breach of Clause 2 was warranted.

Otsuka Pharmaceuticals Europe Ltd, voluntarily admitted that it might have breached the Code with regard to updates to the Jinarc (tolvaptan) summary of product characteristics (SPC). Jinarc was used in certain patients with chronic kidney disease.

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 considered that there might have been a breach of the Code in relation to recent updates to the Jinarc SPC. Otsuka Europe explained that there had been two parallel revisions to the Jinarc SPC since November and these had been communicated to the marketing authorization holder and all relevant European affiliates. They were:

- addition of blister in wallets cards with new marketing authorization numbers – communicated to EU affiliates by Otsuka Europe medical affairs and Otsuka Global Regulatory Affairs Region Europe on 21 December 2018, then with a corrected prescribing information on 10 January 2019 (Case AUTH/3151/1/19 contained details of this issue)
- addition of gout as a common side-effect – communicated as before by Otsuka Europe and Otsuka Global Regulatory Affairs Region Europe to affiliates on 14 February 2019.

In both cases, as well as attaching the revised prescribing information, a word version of the SPC was attached to the notification email to the affiliates, and in the case of Otsuka UK, the word version of the SPC was provided to the electronic Medicines Compendium (eMC) so that the revised SPC could be uploaded. In relation to the marketing authorization holder and wallet blister card revision, Otsuka UK updated the eMC on 4 January 2019 and in relation to the addition of gout, it updated the eMC on 15 February 2019.

On 26 February there was a further copy of the Jinarc SPC emailed by Global Regulatory Affairs Region Europe without Otsuka Europe medical affairs inclusion which stated:

> 'We have now received a confirmation from EMA [European Medicines Agency] to use the consolidated SmPC [summary of product characteristics], including all previous changes in clean version. This will also be published at EMA website (EPAR) [European Public Assessment Report] soon.
>
> Attached you can find the recent consolidated Jinarc approved SmPC (in all languages – clean version) for your implementation where required.'

There were no other attachments to the email other than the SPC.

Otsuka UK queried the email given that the SPC circulated on 14 February had already been implemented, and received the response:

> 'Please replace with new SPC from 25 Feb sent to you today.
> Clarification:
> Two procedures of Jinarc were ongoing in parallel (Wallet and Gout). EMA has approved both SmPCs separately.
> The SmPC from 14 Feb does not includes [sic] last variation of Wallet.'

A preliminary investigation into this by Otsuka Europe medical affairs and Global Regulatory Affairs Region Europe had clarified that the two revisions to the Jinarc SPC were each subject to separate applications to the EMA thus a combined consolidated version had to be approved by the EMA:

- addition of blister in wallets cards
- addition of gout as a common adverse event
- the consolidated SPC of the above mentioned applications (wallet cards and gout).

All three SPCs were approved separately by the EMA and communicated to affiliates according to when the approval was communicated to Global Regulatory Affairs Region Europe. The preliminary investigation concluded that communication to the affiliates on 14 February could have been clearer on this point.

Otsuka Europe regretted that communications to EU affiliates about SPC revisions had caused confusion and that as a result of the actions noted above, there was a Jinarc SPC available on the eMC from 15 February to 1 March (when the consolidated SPC was uploaded following receipt by Otsuka Europe of the word version on 27 February) which contained the latest revision (addition of gout) but not the preceding revision (addition of blister wallet cards). Otsuka Europe was concerned that there might have

been a breach of the undertakings given in Cases AUTH/3041/6/18 and AUTH/3123/11/18, contrary to the requirements of Clauses 9.1 and 2.

Otsuka Europe stated that it also became aware in January 2019 that there was a mistake in the packaging and release of the Jinarc package leaflet at the manufacturing site in the UK, in that the previous version of the package leaflet was packaged with the product. The company notified the EMA and the Medicines and Healthcare products Regulatory Agency (MHRA) on 17 January 2019 about that situation. During the following days the issue was discussed with the EMA. The EMA confirmed on 6 February that no Direct Healthcare Professional Communication (DHPC) was required.

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

RESPONSE

Otsuka Europe stated that communications to its EU affiliates in relation to Jinarc SPC revisions had caused confusion resulting in the Jinarc SPC published on eMC from 15 February 2019 to 1 March 2019 containing the addition of gout but not the preceding revision, the addition of blister wallet cards.

Otsuka Europe stated that the current UK prescribing information for Jinarc (which contained both the addition of blister wallet cards and gout) was, from 15 February 2019 to 1 March 2019, inconsistent with the SPC available on the eMC. Otsuka UK followed the relevant EU process (EU-SOP-MA-002) and its own local process for updating the eMC (OPUK-SOP-RA-001) (copies of the SOPs were provided); the issue was the lack of clarity in the communications from Otsuka Europe in relation to the SPC revisions.

Although Otsuka Europe did not consider that the omission of the blister wallet cards in the SPC was a patient safety issue, the inconsistency amounted to a failure to maintain high standards, in breach of Clause 9.1 and a breach of the undertaking provided in Case AUTH/3041/6/18, in breach of Clauses 29 and 2.

The email sent by Otsuka Global Regulatory Affairs Region Europe on 26 February 2019 did not follow the relevant process in that it was from Global Regulatory Affairs Region Europe only, it did not contain all of the required attachments, and it caused confusion in the affiliates. Causing confusion in a communication formally notifying affiliates about a revision to a SPC amounted to a further failure to maintain high standards, contrary to the requirements of Clause 9.1. Otsuka Europe also considered that causing such confusion was a breach of the undertaking given in Case AUTH/3123/11/18, in breach of Clauses 29 and 2.

Otsuka Europe explained that the version of the SPC (uploaded to the eMC on 4 January) contained the blister wallet card revision, and was replaced on the eMC on 15 February 2019 with the version of the SPC that contained the gout revision but not the blister wallet revision; this was then replaced on the eMC by the consolidated SPC (containing blister wallet and gout revisions) on 1 March 2019. As noted in Otsuka's previous letter, a word version of the SPC was required in order to update the eMC, and this was only provided to Otsuka UK on 27 February 2019. Otsuka Europe provided a timeline to illustrate events.

As noted in Otsuka Europe's previous letter of 12 March 2019, when two or several stand-alone variation applications were being submitted and/or assessed in parallel at the EMA, the procedures would be kept separate. So, in this case it was not possible to avoid having an SPC with gout that did not contain the blister wallet cards. However, if this had been made clear to affiliates when the blister wallet card was approved, they could have planned how to deal with this, for example, by taking advice from the PMCPA.

The lack of clarity in relation to the communication of the various SPC revisions was subject to an open investigation and Otsuka Europe was considering how such communications could be improved in the future. In addition, Otsuka Europe was investigating why the communication of the consolidated SPC did not follow the relevant process.

As Otsuka Europe noted in its letter of 12 March 2019, it had communicated a mistake in the packaging and release of the Jinarc package leaflet at the manufacturing site in the UK where the previous version of the package leaflet was packaged with the product. The manufacturing site was notified on 12 October 2018 of an upcoming revision to the package leaflet with an implementation date of 30 November 2018. That package leaflet revision contained three updates:

- extended contraindication (hypersensitivity to benzazepine or benzazepine derivatives)
- missing adverse drug reaction 'abdominal pain' ('belly pain' in package leaflet)
- missing extension of indication (chronic kidney disease stage 1 to 4 instead of 1 to 3).

The manufacturing site mistakenly used the previous version of the package leaflet starting 30 November 2018. Otsuka identified the issue on 10 January 2019; between the 10 January and 18 February 2019 the manufacturing site identified the same issue in 14 batches (6 UK batches), of which 12 (4 UK batches) were released between 17 December 2018 and 7 February 2019 to avoid out-of-stock situations. Otsuka notified EMA and the Defective Medicines Report Centre (DMRC) at MHRA on 17 January 2019.

On 24 January 2019 EMA requested preparation of a DHCP letter and confirmed that an out-of-stock situation for Jinarc would have a wider implication for safety than release of the product with a superseded package leaflet. EMA agreed

that the batches should not be recalled but further replenishment of stock with the correct package leaflet should be initiated as soon as possible.

On 6 February 2019, EMA confirmed that no DHCP letter was required.

PANEL RULING

The Panel noted Otsuka Europe's submission that there had been two parallel revisions to the Jinarc SPC (addition of blister in wallets cards with new marketing authorization numbers and addition of gout as a common adverse drug reaction) and that the two revisions were each subject to separate applications to the EMA and therefore a combined consolidated version also had to be approved by the EMA.

The Panel noted Otsuka Europe's submission that there was a Jinarc SPC available on the eMC from 15 February to 1 March which contained the addition of gout but not the preceding SPC revision of addition of blister wallet cards and that the UK prescribing information current at that time which contained both the addition of gout and blister wallet cards was therefore inconsistent with the SPC published on the eMC during that time.

The Panel noted, based on Otsuka Europe's submission, that when two or more variation applications were submitted and/or assessed in parallel by the EMA, the procedures were kept separate, and further noted Otsuka Europe's submission that, in this case, having an SPC with gout but without the preceding blister wallet cards revision was unavoidable. However, the Panel noted Otsuka Europe's submission that the communication to the affiliates dated 14 February regarding this matter could have been clearer so they could have planned how to deal with this situation, and that the communication regarding the consolidated SPC sent to the affiliates on 26 February had not followed the relevant SOP including that it did not have all the required attachments and it was from Global Regulatory Affairs Region Europe only and that it caused confusion in the affiliates.

The Panel considered that the lack of clear communication by Otsuka Europe to its affiliates, which was compounded by the failure to follow, and lack of consistent application of, the relevant SOP, meant that Otsuka Europe had failed to maintain high standards and a breach of Clause 9.1 was ruled.

The Panel noted Otsuka Europe's admission regarding the breach of undertakings given in Cases AUTH/3041/6/18 and AUTH/3123/11/18.

The Panel noted that a form of undertaking and assurance was an important document. Companies had to give an undertaking that the material or activity in question and any similar material/activity, 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.

In its response Otsuka Europe explained that the omission of the blister wallet cards in the SPC whilst not a patient safety issue was an inconsistency with the prescribing information that amounted to a failure to maintain high standards in breach of the undertaking given in Case AUTH/3041/6/18.

The Panel noted that in Case AUTH/3041/6/18, Otsuka Europe was found in breach of: Clause 4.1 for promotional materials either missing prescribing information or not containing the latest version of the prescribing information, Clause 9.1 for Otsuka Europe's governance of materials falling below acceptable standards, and Clause 2 for, *inter alia*, not providing prompt communication to Otsuka UK regarding SPC updates and poor governance which the Panel had considered had potential safety implications. Although there was some overlap between Case AUTH/3041/6/18 and the current case, the Panel noted that there were important differences. The subject matter of the former did not include the accuracy of communications about SPC updates in relation to Jinarc. In addition, the Panel noted that whilst Case AUTH/3041/6/18 included the failure to include the latest version of prescribing information on materials, in the current case, Case AUTH/3169/3/19, the situation was somewhat unusual as from 15 February 2019 to 1 March 2019 the prescribing information included the addition of blister wallet cards and gout whereas the SPC published on the eMC during that time omitted blister wallet cards. The voluntary admission in Case AUTH/3169/3/19 did not refer to use of materials with the incorrect prescribing information. The Panel therefore considered, on balance, that the subject matter of the current case was sufficiently different to Case AUTH/3041/6/18 such that there was no breach of the undertaking given in that case. The Panel therefore ruled no breach of Clause 29 and Clause 2 in this regard.

In relation to the admission of a breach of undertaking and Case AUTH/3123/11/18 Otsuka Europe referred to the email for Global; Regulatory Affairs Region Europe dated 26 February 2019 and failure to follow process and causing confusion. In Case AUTH/3123/11/18, Otsuka Europe was found in breach of, *inter alia*, Clause 9.1 for lack of clear and consistent instructions to employees and third parties in relation to SPC changes and Clause 2 for its failure to timely and robustly address inadequacies in this process. The Panel considered that Otsuka Europe's breach of Clause 9.1 for the lack of clear communication to its affiliates and lack of consistent application of the relevant SOP as noted above in the current case (Case AUTH/3169/3/19) meant that it had breached the undertaking given in Case AUTH/3123/11/18. The Panel therefore ruled a breach of Clause 29. 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.

The Panel noted Otsuka Europe's admission in relation to an out-of-date package leaflet being

packaged with Jinarc at the manufacturing site. The Panel noted Otsuka Europe's submission that the manufacturing site was notified on 12 October 2018 of an upcoming revision to the leaflet with an implementation of 30 November 2018 but it mistakenly used the previous version. The Panel considered that Otsuka Europe had been let down by its manufacturing site. The Panel considered that the package leaflet was an important document for patients and such an error meant that Otsuka Europe had failed to maintain high standards and a breach of Clause 9.1 was ruled. The Panel considered that a breach of Clause 2 was a sign of particular censure. The Panel noted that Otsuka Europe had liaised with the European Medicines Agency (EMA) and the Medicines and Healthcare Products Regulatory Agency (MHRA) with regard to this error and noted the actions Otsuka Europe submitted that it had agreed with the EMA on the matter. The Panel considered that, in these particular circumstances, and on balance, no breach of Clause 2 was warranted.

Complaint received **12 March 2019**

Case completed **5 July 2019**