CASE AUTH/3041/6/18 and CASE AUTH/3042/6/18

EMPLOYEE v OTSUKA EUROPE AND OTSUKA UK

Updating prescribing information

An Otsuka employee complained about the company's procedures for updating the summary of product characteristics (SPC) and prescribing information for Jinarc (tolvaptan, used in chronic kidney disease), Samsca (tolvaptan, used in hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion) and Abilify (aripiprazole, used in schizophrenia). Abilify Maintena was a prolonged-release injectable formulation of aripiprazole.

The complainant alleged that due to a lack of process, changes to the SPC and prescribing information had not been communicated to affiliates or third parties on time. The complainant, who referred to updates from 2017 for Jinarc, Samsca and Abilify, considered that patient safety had been placed at risk.

The detailed responses from Otsuka UK and Otsuka Europe are given below.

The Panel noted that Otsuka Europe was the marketing authorisation holder for Jinarc, Samsca and Abilify which were supplied in the UK by Otsuka UK. Otsuka Europe was also the marketing authorisation holder for Abilify Maintena which was supplied in the UK by Otsuka UK and Lundbeck under a co-promotion agreement. It appeared from the various standard operating procedures that Otsuka Europe Development and Commercialisation was responsible for notifying Otsuka Europe of any changes to the SPCs. The Panel considered that it was unclear whether it was Otsuka Europe or Otsuka Europe Commercialisation and Development that was ultimately responsible for communicating the SPC and PIL changes to Otsuka UK. Historically, affiliates were responsible for implementing the changes including updating prescribing information; going forward Otsuka Europe would be responsible for prescribing information updates.

Otsuka UK was responsible for updating the eMC. The Panel noted Otsuka's submission that Otsuka UK and Otsuka Europe each produced and certified the material it used.

Case AUTH/3042/6/18 – Otsuka UK

1 Jinarc

The Panel noted that following a telephone call with the European Medicines Agency (EMA) on 6 January 2017, Otsuka Europe Development and Commercialisation communicated the update to include anuria as a new contraindication in Section 4.3 of the Jinarc SPC to Otsuka Europe and Otsuka UK on 9 January 2017. Otsuka treated this as the start date of formal approval for implementation of the update. Otsuka UK implemented the SPC update but did not send the revised SPC to the eMC until 3

February 2017. The Panel considered that the delay in sending the updated SPC to the eMC meant that Otsuka UK had failed to maintain high standards and a breach of the Code was ruled.

Otsuka UK prepared updated prescribing information on 17 February 2017. The Panel disagreed with Otsuka's submission that this SPC update was not regarded as constituting important safety information requiring adoption of the accelerated prescribing information amendment under the relevant SOP.

The Panel noted Otsuka's submission that new promotional material incorporating the revised prescribing information was issued from 1 March 2017. However, it was of concern that existing promotional material which pre-dated the SPC update was only withdrawn on 29 March 2017 as a routine withdrawal, rather than to ensure compliance with the Code after the SPC update. The Panel noted that the Code listed the components of prescribing information which had to be provided including, *inter alia*, contraindications relevant to the promoted indication. Failure to provide the required information in the prescribing information would be a breach of the Code. The Panel considered that all promotional material that was not withdrawn until 29 March and contained prescribing information that omitted the anuria contraindication and was, therefore, inconsistent with the SPC current at that time, was not up-to-date and was therefore in breach of the Code. The Panel considered that the delay in updating the prescribing information and withdrawing material with out-of-date prescribing information meant that Otsuka UK had failed to maintain high standards and a breach of the Code was ruled.

The Panel noted Otsuka's submission that in April 2018, Otsuka UK discovered that anuria as a contraindication had not been included in certain educational materials required under a risk minimisation plan (RMP). The Panel was concerned to note that the educational material implementing the RMP had still not been updated and submitted to the MHRA for approval at the time of Otsuka's response to this complaint (June 2018). The Panel considered that Otsuka UK had failed to maintain high standards by not promptly updating educational material required under the RMP and a breach of the Code was ruled. The Panel considered that such failures had potential patient safety implications and noted its comments on Clause 2 and ruling on this matter below.

The Panel noted that the CHMP issued a positive opinion on 6 July 2017 to update Section 5.1 of the Jinarc SPC to include clinical trial results from the post-authorisation study, an extension to the TEMPO trial, which evaluated the effects of tolvaptan on, *inter alia*, safety. Otsuka Europe Development and Commercialisation communicated the SPC update to Otsuka Europe and Otsuka UK the same day. The Panel noted Otsuka's submission that the communication was, however, not received by Otsuka UK until November 2017 and Otsuka sent the revised SPC to the eMC on 29 November 2017. The Panel considered that the substantial and unexplained delay in Otsuka UK implementing the SPC change and updating the eMC meant that high standards had not been maintained. A breach of the Code was ruled.

The Panel noted the content of prescribing information and that some changes to an SPC might not need to be reflected in the prescribing information. The Panel noted Otsuka's view that this SPC revision had not necessitated a change to the prescribing information. The complainant bore the burden of proof and, in the Panel's view, he/she had not

established that the SPC update necessitated a change to the prescribing information. The Panel therefore ruled no breach of the Code.

The Panel noted that whilst fluconazole had been listed as a moderate CYP3A inhibitor in Section 4.5 of the Jinarc SPC since marketing authorisation was granted in May 2015, the CHMP issued a positive opinion on 12 April 2018 to include additional information regarding the co-administration of tolvaptan and fluconazole. Otsuka Europe Development and Commercialisation communicated the SPC change to Otsuka Europe and Otsuka UK on 16 April 2018. Otsuka UK implemented the update and sent the revised SPC to eMC on 25 April 2018. The Panel did not consider that Otsuka UK had failed to maintain high standards in this regard and no breach of the Code was ruled.

The complainant bore the burden of proof and, in the Panel's view, he/she had not established that the SPC update necessitated a change to the prescribing information. The Panel therefore ruled no breach of the Code.

The Panel noted Otsuka's submission that, upon review of its materials, a number of Jinarc RMP training materials and health professional guides did not contain the dose adjustment required as a result of the Jinarc SPC update in relation to the interaction with fluconazole. The Panel further noted, with concern, that on its examination of the SPCs, the Jinarc dose reduction recommendation for patients taking moderate CYP3A inhibitors, including fluconazole, appeared to have been in the SPC since the grant of the marketing authorisation in May 2015, rather than April 2018 as implied by Otsuka, and thus the company's submission on this point was incorrect. The Panel was concerned to note Otsuka's submission that the RMP material had yet to be updated and submitted to the MHRA at the time of Otsuka's response to this complaint and considered that Otsuka had failed to maintain high standards by not promptly updating educational material required under the RMP. A breach of the Code was ruled. The Panel considered that such failures had potential patient safety implications and noted its comments on Clause 2 and ruling on this matter below.

2 Samsca

The Panel noted Otsuka's submission that the European Commission decision to update the Samsca SPC to include the 7.5mg dosage form and update the undesirable effects, posology and method of administration was adopted on 18 September 2017. The update included the change in incidence of an adverse event, rapid correction of hyponatraemia (RCHN) from common to very common and a recommendation to use a lower dose in patients susceptible to RCHN.

Otsuka Europe Development and Commercialisation communicated the update to Otsuka Europe and Otsuka UK on 20 September 2017. The Panel noted Otsuka's submission that the notification was sent to the incorrect person at Otsuka UK and was therefore not received. The communication was re-sent to Otsuka UK on 21 November 2017. Otsuka UK implemented the SPC update but did not send the revised SPC to the eMC until 8 January 2018. The Panel considered that the delay in implementing this SPC update and sending it to the eMC meant that high standards had not been maintained. A breach of the Code was ruled. The Panel noted the nature of the SPC update and considered that such failures had potential patient safety implications. The Panel noted its comments on Clause 2 and ruling on this matter below.

The Panel was concerned to note Otsuka's submission that existing promotional material, which pre-dated the SPC update, was only withdrawn on 4 December 2017. The Panel noted, however, Otsuka's submission that no promotional activity took place between the end of September 2017 and February 2018 and so, in Otsuka's view, there was no requirement to revise the prescribing information when the SPC was updated. The Panel queried why, if the material was not being used, it was not withdrawn sooner. The Panel noted that Otsuka had not commented on any applicable online promotional materials such as those available on websites. The Panel noted Otsuka's submission that the prescribing information was ultimately revised on 9 January 2018, before promotion started in February 2018 and promotional material incorporating changes following the SPC update was first issued on 18 March 2018.

Whilst the Panel had concerns, it noted that there was no evidence before it that material with out-of-date prescribing information had been distributed or was available online. The complainant had provided insufficient evidence to discharge the burden of proof on the balance of probabilities; no breach of the Code was ruled. The Panel considered, however, that failure to withdraw such material to ensure it could not be used meant that Otsuka had failed to maintain high standards and a breach of the Code was ruled.

3 Abilify and Abilify Maintena

The Panel noted Otsuka's submission that the CHMP issued a positive opinion on 26 October 2017 and recommended approval of an SPC update for Abilify and Abilify Maintena to add specific warnings related to impulse control disorder, binge eating, compulsive shopping and poriomania.

The Panel noted Otsuka's submission that the date the linguistic review ended (4 December 2017) was the SPC update implementation date and Otsuka Europe Development and Commercialisation communicated the SPC update to Otsuka Europe and Otsuka UK on 7 December 2017. The revised SPCs for the various Abilify formulations were sent to the eMC between 25 January 2018 and 5 February 2018. The Panel considered that the delay in updating the eMC with the SPC change, which included additional information in Section 4.4 (special warnings and precautions for use) and the addition of new adverse drug reactions to Section 4.8 meant that high standards had not been maintained and a breach of the Code was ruled. The Panel considered that such failures had potential patient safety implications and noted its comments on Clause 2 and ruling on this matter below.

The Panel was concerned to note Otsuka's submission that this SPC update would generally have prompted update of promotional material in line with standard SOP timelines (within 6 months of formal approval and not later than implementation of updated PIL in finished product packs). Revision was carried out in accordance with accelerated timelines only because review of the prescribing information indicated that improvement was needed irrespective of the SPC update.

The Panel noted that the general principle was that prescribing information must be up-to-date, must comply with the Code and must be consistent with the SPC.

The Panel noted, however, Otsuka's submission that existing promotional material, which pre-dated the SPC update, was withdrawn on 28 November 2017. No promotional material was issued between 4 December 2017 (date SPC update approved) and 11 December 2017 (date prescribing information revised). The Panel, therefore, ruled no breach of the Code.

The Panel noted that there was an update to Section 6.1 of the Abilify oral solution SPC regarding a change of flavour. The Panel noted Otsuka's submission that the update did not require European Commission approval; EMA confirmed the validity of the submission and issued a positive opinion on 26 March 2018.

Otsuka Europe Development and Commercialisation communicated the SPC update to Otsuka Europe and Otsuka UK on 28 March. The update was, however, sent to an individual Otsuka UK employee who was on annual leave at the time rather than to the designated UK regulatory inbox.

Otsuka UK sent the revised SPC to the eMC on 24 April 2018. The Panel was particularly concerned to note that this delay occurred despite Otsuka's submission that a task force to implement corrective and preventative measures was put in place in February 2018, after an Otsuka UK employee had raised concerns about the company process in November 2017. The Panel considered that high standards had not been maintained and ruled a breach of the Code.

The Panel noted that the complainant had not established that the SPC update necessitated a change to the prescribing information. No breach of the Code was ruled.

The Panel noted Otsuka's submission that it had reviewed Otsuka UK Jinarc, Samsca, Abilify and Abilify Maintena materials certified from 1 January 2017 and had identified materials that did not contain the latest version of prescribing information and materials that were missing prescribing information. The Panel noted that Otsuka might have been referring to what it considered to be the latest version of the prescribing information; given its ruling above the Panel considered that what Otsuka considered to be the latest version of prescribing information might not have met the requirements of the Code. The Panel further queried whether the search criteria adopted by Otsuka captured all affected materials in scope of the complaint. In relation to the materials that Otsuka submitted did not contain the latest version of prescribing information the Panel considered that in relation to Jinarc its ruling above appeared to cover this matter and it made no further ruling. In relation to Abilify Maintena materials that Otsuka submitted did not contain the latest version of prescribing information the Panel ruled a breach of the Code. A breach of the Code was ruled in relation to each of the materials noted above that Otsuka submitted were missing prescribing information. High standards had not been maintained and a breach of the Code was ruled. The Panel considered that such failures had potential patient safety implications and noted its comments on Clause 2 and ruling on this matter below.

The Panel noted that it was crucial that health professionals and others could rely upon the industry for up-to-date and accurate information about medicines. The Panel was concerned to note Otsuka UK's failures to implement SPC changes and to promptly: update the eMC website; update prescribing information; withdraw materials including promotional material with out-of-date prescribing information; and update and submit

material required under the RMP to the MHRA. The Panel noted its comments above with regard to materials with potential patient safety implications as a result of such failures.

The Panel was particularly concerned about the volume of educational material required under the Jinarc RMP that had not been updated and submitted to the MHRA for approval at the time of Otsuka's response to this complaint. The Panel was concerned that Otsuka only appeared to have become aware of this when responding to this complaint and was further concerned that its submission about when the Jinarc dose adjustment for patients taking fluconazole first appeared in the SPC was incorrect. It was important, and fundamental to self-regulation, that companies submitted accurate information when responding to complaints.

The Panel considered that such failures brought discredit upon, and reduced confidence in, the pharmaceutical industry. 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 new information, the omission of which could potentially impact patient safety. A breach of Clause 2 was ruled.

The Panel noted that Otsuka was trying to address the issues in question. Despite such efforts, it was clear that governance issues remained. The Panel noted the breadth and depth of the company's compliance difficulties. In the Panel's view, it was likely that the compliance issues went beyond matters that arose from the narrow set of materials identified by Otsuka in response to this complaint and beyond matters raised by the complainant. The Panel noted that its brief review of the company's SOPs raised further concerns in relation to governance. In addition, the Panel noted that some Jinarc RMP materials appeared to contain incorrect information. The Panel considered that its concerns in relation to this case and broader concerns about the company's governance warranted reporting Otsuka UK to the Appeal Board under Paragraph 8.2 of the Constitution and Procedure for the Appeal Board to consider in relation to Paragraph 11.3 of the Constitution and Procedure.

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Case AUTH/3041/6/18 Otsuka Europe

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 it was unclear from Otsuka's submission what actions Otsuka Europe had taken when notified of each SPC update by Otsuka Europe Development and Commercialisation. It was of concern that no information was given about withdrawal of materials by Otsuka Europe.

The Panel noted Otsuka's submission that Otsuka Europe produced and certified the materials it used. The Panel noted Otsuka's submission that upon review of all Jinarc, Samsca, Abilify and Abilify Maintena materials certified from 1 January 2017 that required prescribing information and were issued by Otsuka Europe and used in the UK and/or with UK health professionals it identified 7 Jinarc promotional materials issued by Otsuka Europe related to a website that did not contain the latest version of the

prescribing information. The Panel ruled breaches of the Code in relation to each of these materials.

The Panel noted the complainant bore the burden of proof and had not established that any Samsca material issued by Otsuka Europe since 1 January 2017 contained out-of-date prescribing information. The Panel thus ruled no breach of the Code.

The Panel noted Otsuka's submission that it had not identified any Abilify or Abilify Maintena materials issued by Otsuka Europe that did not contain the latest version of prescribing information, however, it had identified two Abilify Maintena materials that were missing prescribing information and a breach of the Code was ruled in relation to each.

In the Panel's view, and noting its rulings above, governance of materials at Otsuka Europe had fallen below acceptable standards. The Panel considered that high standards had not been maintained and a breach of the Code was ruled.

The Panel noted instances where Otsuka UK had not received prompt communication from Otsuka Europe regarding an SPC update because the notification was sent to the incorrect person or to an individual who was on leave rather than to a designated UK regulatory inbox. The Panel noted its comments and rulings above in Case AUTH/3042/6/18. The Panel also considered that certain comments above at Case AUTH/3042/6/18 were relevant in relation to poor governance by Otsuka Europe. The Panel considered that the failures had potential patient safety implications as noted in Case AUTH/3042/6/18. It was crucial that health professionals and others could rely completely upon the industry for up-to-date and accurate information about medicines. The Panel considered on balance that the cumulative effect of its rulings and comments above brought discredit upon and reduced confidence in the pharmaceutical industry and warranted a ruling of a breach of Clause 2 and ruled accordingly.

The Panel considered that, in general, and noting its comments and rulings above, Otsuka Europe's overall governance in relation to its processes and materials above appeared to be poor. The Panel noted Otsuka's submission that processes fell short of expected high standards and the time for remediation was too long. The Panel was concerned that confirmation of implementation of SPC and PIL updates was apparently not recorded prior to June 2018.

Although it appeared from its submission that Otsuka Europe was trying to address some of the issues in question, the Panel considered that its concerns in relation to this case warranted reporting Otsuka Europe to the Appeal Board under Paragraph 8.2 of the Constitution and Procedure for the Appeal Board to consider in relation to Paragraph 11.3 of the Constitution and Procedure.

The Appeal Board noted the Panel's comments and rulings of breaches of Clauses of the Code in Cases AUTH/3041/6/18 and AUTH/3042/6/18, including its decision to report Otsuka Europe and Otsuka UK to the Appeal Board. The Appeal Board noted that Otsuka Europe and Otsuka UK had provided detailed information about their compliance difficulties and they had apologised.

The Appeal Board noted the timelines provided showing European remediation to date from March 2018. It appeared from questioning the company representatives that little activity had taken place following the internal audit in September 2016 and when the issue was raised internally in November 2017. It was only after the complaint was made to the PMCPA in June 2018 that action was taken. This raised concerns about how seriously the company took the issue, its impact on patient safety and the culture at Otsuka. The company representatives stated that the delay was due to a lack of understanding of the seriousness and importance of the process. There was a lack of communication across the company. Senior leaders had apologised to employees. Speak-up processes had been introduced and more was shared about reporting incidents.

The Appeal Board noted the company's submission that it recently had another internal audit of its end-to-end processes and it was awaiting that report. The company representatives referred to the CORE programme which started in February 2019 led by the UK. The CORE programme had 4 elements; culture and compliance, one organisation, ready for audit and everybody was responsible for compliance. The company representatives also referred briefly to other issues identified mentioning meetings and congresses. These would be prioritised. Otsuka UK referred to a new meetings process.

The Appeal Board was very concerned that an overall failure of governance in relation to Otsuka Europe and Otsuka UK's processes in implementing SPC changes, updating prescribing information, updating and withdrawing promotional materials, and the update and submission to the MHRA of its risk minimisation materials in a timely manner had potential patient safety implications. It was crucial that health professionals and others could rely completely upon the industry for up-to-date and accurate information about its medicines. The Appeal Board noted Otsuka UK and Otsuka Europe's submission that they were now putting systems and processes in place to address these issues. The Appeal Board noted the scale of the task but queried whether this was being done sufficiently quickly given the seriousness of the matter.

The Appeal Board decided that in accordance with Paragraph 11.3 of the Constitution and Procedure, Otsuka Europe and Otsuka UK should be publicly reprimanded for the failures to implement SPC changes and update impacted materials in a timely manner which had potential to impact patient safety. The Appeal Board also decided to require audits of Otsuka Europe and Otsuka UKs' procedures in relation to the Code in Cases AUTH/3041/6/18 and AUTH/3042/6/18. These audits should take place by mid July 2019. The audits would take place at the same time as that required in Case AUTH/3123/11/18. On receipt of the report of the audits, the Appeal Board would consider whether further sanctions were necessary.

On receipt of the report for the July 2019 audits the Appeal Board was very concerned to note the extent of the companies' failings including that there was a systemic lack of governance shown by the failure to take action in these cases. Leadership and communication needed to be improved urgently. The governance from Japan to Europe and from Europe to UK needed huge improvement. There appeared to be longstanding failures in this regard, particularly in relation to holding senior individuals to account.

The Appeal Board noted that the report of the audits highlighted a number of concerns including that existing senior staff needed to improve their knowledge and leadership on compliance matters, engage with and ensure that all staff understood its importance. Staff should be helped and encouraged to improve their skills in relation to matters covered by the Code. Significant commitment was required to address the issues.

The Appeal Board noted from the report of the audits that Otsuka Europe had not provided accurate information about the training of the SOPs to the Appeal Board in March 2019 when the reports from the Panel were considered. The Appeal Board noted that self-regulation relied upon, *inter alia*, the provision of complete and accurate information from pharmaceutical companies. The Appeal Board decided that in accordance with Paragraph 11.3 of the Constitution and Procedure, Otsuka Europe should be publicly reprimanded for providing inaccurate information to the Appeal Board.

The Appeal Board noted Otsuka's compliance plan and decided that Otsuka should provide a detailed written account of its progress by the end of November 2019. It was vital that swift comprehensive action was taken and noting the failure to take appropriate action over a long period of time, the Appeal Board considered that given the exceptional circumstances of this matter, including the scale and seriousness of the difficulties at Otsuka, it would be helpful if Otsuka representatives attended the December 2019 meeting of the Appeal Board to discuss the progress and future plans. The Appeal Board noted that both Otsuka Europe and Otsuka UK had set themselves a number of compliance objectives and considered that sufficient time would be needed for these to be completed in order for any meaningful progress to be assessed. The Appeal Board decided that both Otsuka Europe and Otsuka UK should be re-audited in early 2020. At its meeting in December the Appeal Board would decide the timing of the re-audits and on receipt of the report for the re-audits it would decide whether further sanctions were necessary.

At its meeting in December 2019 representatives from Otsuka Europe and Otsuka UK attended to discuss the progress and future plans. The companies welcomed the opportunity to provide the Appeal Board and PMCPA with a written account of the activities conducted and progress made since receipt of the report of the audits. The Appeal Board noted that whilst there was a lot of work to be done, a number of activities and actions were completed, planned and/or in process. On the information before it the Appeal Board decided that the re-audits should take place in April 2020 at which point it expected substantial improvements. On receipt of the report for the re-audits it would decide whether further sanctions were necessary.

On receipt of the report for the April 2020 re-audits the Appeal Board noted the difficulties of conducting audits remotely and that there was little new activity due to the continuation of the 'pencils down'/'deprioritisation' policies. The Appeal Board considered that there had been some progress and it appeared that things were now heading in the right direction. There had been changes with new staff and new members of the Otsuka Board as well as additional resource for compliance and compliance objectives had been introduced. Key senior staff still needed to continue to develop their leadership on compliance. The Appeal Board noted that whilst most staff understood the reasons for the re-audits; it was concerned that some staff still did not. Otsuka UK and Otsuka Europe needed to continue to improve working relationships, including in and

between the medical departments. It appeared that communication with Japan had improved. There was to be a staff survey in late 2020.

The Appeal Board noted that further improvement was required, the report of the re-audits highlighted a number of areas on which to focus.

The Appeal Board decided that Otsuka UK and Otsuka Europe should be re-audited in April 2021 at which point it also expected the companies to demonstrate continued progress and improvement. On receipt of the of the report for the re-audits the Appeal Board would decide whether further sanctions were necessary.

On receipt of the report for the April 2021 re-audits the Appeal Board noted that there had been some further progress and it appeared that matters were continuing to head in the right direction. However, the Appeal Board considered that the pace of improvement needed to accelerate. Otsuka UK and Otsuka Europe needed to continue to improve working relationships, including in and between the medical departments. Senior staff needed to work together to continue to improve their knowledge and leadership on compliance. The Appeal Board noted that further improvement was required, the report of the re-audits highlighted a number of areas on which to focus. The Appeal Board decided that Otsuka UK and Otsuka Europe should be re-audited in December 2021/January2022 at which point it expected the companies to demonstrate continued progress and embedded improvement. On receipt of the report for the re-audits the Appeal Board would decide whether further sanctions were necessary.

On receipt of the report for the January 2022 re-audits the Appeal Board noted that Otsuka had continued to build on the improvements described in the report of the 27 and 28 April 2021 re-audits. It was important that progress on company culture continued such that there was a team approach both within each company and between each company.

The Appeal Board noted that the report of the January 2022 re-audits still highlighted work to be done and it was important that these were addressed.

The Appeal Board considered that from the report of the January 2022 re-audits it appeared that there had been further progress. The Appeal Board was concerned that it had taken 4 audits/re-audits to get to this stage.

The Appeal Board noted that Otsuka had a compliance CORE tracker to address recommendations from the re-audits. On the basis that this work was completed, the progress shown to date was continued and commitment to compliance was maintained, the Appeal Board decided that no further action was required.

In Cases AUTH/3041/6/18 and AUTH/3042/6/18, an employee of Otsuka complained about the company's procedures for updating the summary of product characteristics (SPC) and prescribing information for Jinarc (tolvaptan, used in chronic kidney disease), Samsca (tolvaptan, used in hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion) and Abilify (aripiprazole, used in schizophrenia). Abilify Maintena was a prolonged-release injectable formulation of aripiprazole.

COMPLAINT

The complainant alleged that due to a lack of process, changes to the SPC and prescribing information had not been communicated to affiliates or third parties on time. The complainant, who referred to updates from 2017 for Jinarc, Samsca and Abilify, considered that patient safety had been placed at risk.

When writing to Otsuka, the Authority asked it to bear in mind the requirements of Clauses 2, 4.1, 4.2 and 9.1 of the Code.

RESPONSE

One response was provided on behalf of both Otsuka Europe and Otsuka UK. Otsuka explained that the organisation in the UK was comprised of several legal entities:

- Otsuka Pharmaceutical Europe Ltd – was the marketing authorisation holder for the products listed in the complaint.
- Otsuka Pharmaceuticals (UK) Ltd – was the commercial operation for Otsuka activities in the UK.
- Otsuka Europe Development and Commercialisation Ltd – was incorporated in the UK and provided quality, safety and regulatory affairs services (eg marketing authorisation applications, variations, any labelling etc.); it was the company where the EU Qualified Person for Pharmacovigilance resided and where the Pharmacovigilance System Master File was located (both based in Germany).

Otsuka stated that it took patient safety extremely seriously; it had conducted a thorough review of its processes and acknowledged the following:

- processes for implementation of updates to SPCs fell short of expected high standards regarding clear and consistent communication of the actions required about updates to prescribing information;
- processes were not always consistently followed;
- some of the historical prescribing information and materials in the UK did not meet the highest standards;
- SPC and patient information leaflet uploads to the electronic medicines compendium (eMC) website were delayed in Otsuka UK;
- the time for remediation was too long.

Otsuka noted that an initial concern was raised in November 2017 by an Otsuka UK employee. Since then, corrective and preventative measures had been put in place to ensure that the issues listed above would not be repeated. Significant changes had been made and these were summarised below. A task force was initiated in February 2018 to further address these issues and implement additional corrective measures.

Otsuka submitted that its review had unfortunately shown a number of deficiencies in relation to implementation of updates to SPCs and subsequent incorporation of prescribing information. A detailed review of its safety database had shown no evidence of an increase in product-related adverse events in relation to these updates, however, the company could not completely exclude the potential risk to patients.

After recognising the deficiencies referenced above, Otsuka stated that it had acted to address them. The prescribing information currently used by Otsuka Europe or Otsuka UK in all materials in the UK for Jinarc, Samsca and Abilify, was up-to-date and compliant. All promotional material issued in the UK by the two companies reflected the current SPC and prescribing information for the relevant product. Promotional material which no longer met those standards had been withdrawn.

However, while the current position with respect to implementation of SPC updates was compliant, Otsuka was aware that communication between Otsuka Europe, Otsuka Europe Development and Commercialisation and affiliates and third parties in the past, had not always been as effective as it should have been, with resulting delay in implementing updates, specifically on several occasions in relation to the addition of revised versions of updated SPCs onto the electronic medicines compendium (eMC). In February 2018 Otsuka Europe recognised that processes were less robust than intended, long before the complaint was sent to the PMCPA and a task force was established by Otsuka Europe to investigate the issues and institute corrective measures. The work of the task force and the remediation programme which was being put in place was widely communicated within Otsuka Europe and Otsuka UK from March 2018.

Otsuka stated that it had investigated the cause of the communication issues identified above. In particular, it had established that the issues that had been identified were generally attributable to one or more of the following:

- the existing process for communicating SPC updates was not consistently followed;
- communication of update information to individuals within the organisations (rather than to a designated regulatory inbox) meant that communications could be missed if the person was absent from work or had left the organisation;
- simple misdirection of communications to the wrong recipient who would then not know how to handle them;
- timelines for completion of actions were not, in all cases, specified when information was sent to the affiliate;
- no confirmation back to Otsuka Europe by the affiliate to confirm receipt and action.

Following this investigation, Otsuka stated that in early 2018 it had instituted corrective measures, including improved procedures and updates to existing SOPs, intended to strengthen its processes and to ensure that the delays it had recognised and acted upon, did not occur in the future. A standard operating procedure (SOP) which covered communication of SPC updates by Otsuka Europe to affiliates, was temporarily withdrawn in March 2018; this withdrawal was an error of judgement. Otsuka submitted that a guidance document covering those procedures was put in place on 7 June 2018 as an interim solution.

The standard operating procedures and other process documents in place from 1 January 2017

Otsuka stated that the SOPs and other process documents listed (copies provided) were relevant to communications between Otsuka Europe, Otsuka Europe Development and Commercialisation, Otsuka UK and third parties in relation to SPC updates and to implementation of changes in the UK. Otsuka provided a summary of the process as provided in the various SOPs.

History of SPC updates for Jinarc, Samsca and Abilify from 1 January 2017

Jinarc and Samsca were supplied in the UK by Otsuka UK under EU marketing authorisations held by Otsuka Europe. Abilify was supplied in oral and intramuscular formulations (Abilify) and as a long-acting injectable formulation (Abilify Maintena) which were also supplied under EU marketing authorisations held by Otsuka Europe. Abilify was supplied in the UK by Otsuka UK. Abilify Maintena was supplied in the UK under a co-promotion agreement by Otsuka UK and Lundbeck.

Copies of the SPCs and corresponding prescribing information for Jinarc, Samsca, Abilify and Abilify Maintena, effective during the period from 1 January 2017 to date were provided. Following notification of an SPC update, consideration was given to whether a corresponding amendment to the prescribing information was required, in accordance with the provisions of Clause 4.2 of the Code. Prescribing information would also be reviewed and might be updated for quality reasons between SPC updates. The review and revision of prescribing information was previously carried out in the UK by Otsuka UK, however, under the updated procedures (currently reflected in the guidance document provided) Otsuka Europe was responsible for preparing and updating prescribing information centrally and distributing this to affiliates.

A chronology of the various SPC updates covering the period from 1 January 2017 to date was summarised below:

Jinarc

TYPE II VARIATION • Section 4.3: Addition of anuria as contraindication EMA Assessment: Standard timelines MAH Implementation: Standard timelines	SPC Update: The Committee for Medical Products for Human use (CHMP) issued a positive opinion and recommended an update to the SPC on 15 September 2016. This was a type II variation to the marketing authorisation, introducing a new contraindication, for which formal approval by the European Commission was a standard requirement. However, when Otsuka Europe Development and Commercialisation contacted the European Medicines Agency (EMA) on 6 January 2017 by telephone to ask when the variation would be approved, Otsuka submitted that the EMA indicated that it considered the update to be so minor (not considered a new contraindication, but simply new wording emphasising the existing safety information), that Otsuka should proceed to implement immediately, without waiting for Commission approval. Otsuka Europe Development and Commercialisation communicated this revised implementation requirement to Otsuka Europe and Otsuka UK on 9 January 2017, which was therefore treated as the starting date of formal approval for implementation of this SPC update. This communication took place within the two business days specified in EU-SOP-RA-002v5. On 24 January 2017 the EMA confirmed in writing the information already provided by telephone on 6 January 2017.

	Otsuka UK implemented the SPC update but did not send the revised SPC to the eMC until 3 February 2017 (25 days after the date of notification by Otsuka Europe Development and Commercialisation). This was outside the 10 working days specified in OPUK-SOP-MA-010.6.0. Updated prescribing information: Updated prescribing information was prepared on 17 February 2017 (39 days after the date of notification of the SPC update by Otsuka Europe Development and Commercialisation). While the SPC update represented the addition of a contraindication, Otsuka submitted that the EMA viewed the change as minor; the product was indicated only in patients with stages 1-3 chronic kidney disease (who would not be anuric), the SPC had previously included a recommendation, under 'precautions and warnings', that urinary output should be secured. Additionally, the SPC had previously included a recommendation in the 'posology' section, to discontinue use of the product if renal insufficiency progressed to chronic kidney disease stage 5, which could result in anuria. Otsuka stated that, in these circumstances, the SPC update was not regarded as constituting important safety information requiring accelerated amendment to promotional material and the revision of the prescribing information was completed within the six month period specified in OPUK-SOP-MA-010.6.0 for standard amendments. Promotional material: Existing promotional material which pre-dated the SPC update was withdrawn on 29 March 2017 as a routine withdrawal under EU-SOP-MA-010 v1.0 (79 days after the date of formal approval). New promotional material incorporating the revised prescribing information was issued from 1 March 2017. Non-promotional material: Educational material implementing the risk minimisation plan for Jinarc had not yet been updated; the material was currently being updated and would be sent to the MHRA for approval. Patient safety implications: The SPC update did not constitute an emerging safety issue or an urgent safety restriction. Otsuka submitted that anuria was a rare condition and prescribers who used Jinarc knew about its aquaretic properties and about the information that was already in the SPC before the update to indicate the proper use of Jinarc. A detailed review of the safety database showed no evidence of an increase in

	product-related adverse events in relation to these updates, however, Otsuka could not completely exclude the potential risk to patients.
TYPE II VARIATION • Section 5.1: Inclusion of clinical trial results from the post authorisation efficacy study, extension to the TEMPO trial EMA Assessment: Standard timelines MAH Implementation: Standard timelines	SPC update: The CHMP issued a positive opinion and recommended an update to the SPC on 6 July 2017. Otsuka Europe Development and Commercialisation communicated the SPC update to Otsuka Europe and Otsuka UK on 6 July 2017 within the two days specified in EU-SOP-MA-002v3. Unfortunately, the communication was not received by Otsuka UK until November 2017. Otsuka UK sent the revised SPC to the eMC on 29 November 2017 (146 days after the date of notification by Otsuka Europe Development and Commercialisation). This was outside the 10 working days specified in OPUK-SOP-MA-010.6.0. Updated prescribing information: There was no requirement to revise the prescribing information following the SPC update. Promotional material: The promotional material for Jinarc was not affected by the SPC update. Patient safety implications: The SPC update did not constitute an emerging safety issue or an urgent safety restriction. There were no patient safety implications associated with this SPC update.
TYPE II VARIATION • Section 4.5: Addition of drug interaction (fluconazole) MA Assessment: Standard timelines MAH Implementation: Standard timelines	SPC update: The CHMP issued a positive opinion and recommended an update to the SPC on 12 April 2018. Otsuka Europe Development and Commercialisation informed Otsuka Europe and Otsuka UK and additionally Otsuka Europe medical communicated the SPC update to Otsuka UK on 16 April 2018 (four days after the date of formal approval) within the two business days specified in EU-SOP-MA 002.03, when this was in effect.

	Otsuka UK implemented the SPC update and sent the revised SPC to the eMC on 25 April 2018 (nine days after the date of notification by Otsuka Europe Development and Commercialisation and Otsuka Europe) within the 10 business days specified in OPUK-SOP-MA-010.6.0 Updated prescribing information: There was no requirement to revise the prescribing information following the SPC update. Promotional material: The promotional material for Jinarc (see below, patient safety implications) was not affected by the SPC update. Patient safety implications: The SPC update did not constitute an emerging safety signal or an urgent safety restriction. The update related to a warning regarding an interaction between Jinarc and fluconazole. Co-administration of Jinarc and fluconazole resulted in increased serum levels of Jinarc. Before the update, the SPC already included information about interactions with CYP3A inhibitors, including ketoconazole, a compound related to fluconazole. In these circumstances, Otsuka UK concluded that no amendment to the prescribing information was necessary following the update.

<u>Samsca</u>

EXTENSION APPLICATION • Addition of 7.5mg dosage form • Updates to the undesirable effects (incidence of rapid correction of hyponatraemia (RCHN)) and posology and method of administration (to recommend a lower dose in patients susceptible to	SPC update: The European Commission decision approving the changes was adopted on 18 September 2017. Otsuka Europe Development and Commercialisation communicated the SPC update to Otsuka Europe and Otsuka UK on 20 September 2017, 2 days after the date of formal approval and within the period specified in SOP-EU-MA-002.03. However, notification was sent to the incorrect person at Otsuka UK and was not, therefore, received. Following a routine cross-check by Otsuka UK medical affairs, Otsuka Europe Development and Commercialisation was asked to re-send the communication to Otsuka UK on 21 November 2017. Otsuka UK implemented the SPC update but did not send the revised SPC to the eMC until 8 January 2018 (48 days after

RCHN) at sections 4.2 and 4.8 MA Assessment: Standard timelines MAH Implementation: Standard timelines	the date of notification by Otsuka Europe). This was outside the 10 business day period specified in OPUK-SOP-MA-010.6.0 Updated prescribing information: Otsuka submitted that there was no requirement to revise the prescribing information when the SPC was updated as no promotional activity took place between the end of September 2017 and February 2018. The prescribing information was ultimately revised on 9 January 2018, before promotion started in February 2018. Promotional material: Existing promotional material which pre-dated the SPC update was withdrawn on 4 December 2017, as a routine withdrawal under EU-SOP- MA-010 v1.0 (77 days after the date of formal approval) even though the product was not promoted between the end of September 2017 and February 2018. Promotional material incorporating changes following the SPC update were first issued on 18 March 2018. Patient safety implications: Otsuka submitted that the SPC update did not constitute an emerging safety issue or an urgent safety restriction. The occurrence of RCHN was an already known adverse drug reaction, included in the Samsca SPC before the update. Similarly, requirements for monitoring fluid and electrolyte balance in all patients were present before the update. A review of safety data indicated that one report of RCHN was received before the SPC update approval; however, no such reports were received during the implementation period or for three months after the SPC update had been implemented. Otsuka knew of two cases, one before the SPC update and one during the implementation period, where sodium increasing agents were administered concomitantly with Samsca. Such use was, however, off-label and neither patient developed RCHN. Otsuka further submitted that in circumstances where the update concerned an already known adverse drug reaction, the degree to which the delay in implementation of the update might have posed safety risks to patients appeared to be limited. Considering data from spontaneous safety reports before, during and after the implementation of the SPC update, there was no indication that patients might actually have suffered adverse effects from these delays.

Abilify and Abilify Maintena

TYPE II VARIATION • Section 4.8: Addition of specific warnings relating to impulse control disorder, binge eating, compulsive shopping and poriomania MA Assessment: Standard timelines MAH Implementation: Standard timelines	SPC update: The CHMP issued a positive opinion and recommended approval of an update to the SPC on 26 October 2017. The linguistic review ended on 4 December 2017, which was accordingly the date when implementation could commence. Otsuka Europe Development and Commercialisation communicated the SPC update to Otsuka Europe and Otsuka UK on 7 December 2017, three days after the date of formal approval and outside the two day period specified in EU-SOP-MA-002.03. Lundbeck was notified of the SPC update on 11 December 2017, in accordance with OPUK-SOP-MA-010 v6.0, and confirmed receipt. Otsuka UK sent the revised SPCs for the various Abilify formulations to the eMC between 25 January 2018 and 5 February 2018 (49-60 days after the date of notification by Otsuka Europe Development and Commercialisation). This was outside the 10 business day period specified in OPUK-SOP-MA- 010.6.0. Updated prescribing information: Updated prescribing information was prepared on 11 December 2017, 7 days after the date of formal approval of the SPC update and within the 10 business days specified in OPUK-SOP-MA-010.6.0. Otsuka submitted that although the SPC update was not mandated by CHMP, Otsuka had requested the addition of further warnings to maintain consistency with the core data sheet, in circumstances where the SPC already included a warning about compulsive gambling, a form of impulse control disorder. This SPC update would generally have prompted the update of promotional material in line with standard timelines under EU-SOP-MA-002.03 (within 6 months of formal approval and not later than implementation of updated patient information leaflet in finished product packs). However, review of the existing prescribing information at this stage indicated that improvement was needed irrespective of the SPC update. The revision of the prescribing information was thus carried out in accordance with accelerated timelines. Promotional material:

	Existing promotional material which pre-dated the SPC update was withdrawn on 28 November 2017, prior to notification of formal approval. No promotional material was issued between 4 December when the SPC update was approved and 11 December when the prescribing information was revised. New promotional material incorporating the revised prescribing information was issued from 29 December 2017. Patient safety implications: The SPC update did not constitute an emerging safety issue or an urgent safety restriction. Otsuka stated that it considered reports indicating adverse events that fell under impulse control disorder (higher level term in MedDRA 18.1) and identified six reports of cases, one in patients on Abilify Maintena and five on Abilify, in the year before the SPC update; however, for the period during implementation it identified no cases for any patient on either Abilify Maintena or Abilify and only one case for patients on Abilify after implementation of the eMC revision. Otsuka noted that the event reported in the latter case concerned an adverse drug reaction which was already identified as such in the SPC before the label update. There was accordingly no indication from spontaneous reporting that suggested that patients actually suffered adverse events due to the delay.
TYPE IA_{IN} VARIATION • Section 6.1 Change of flavour (Abilify oral solution) EMA Assessment: Not applicable. For type IA variations there is only validation, no scientific assessment MAH Implementation: Standard timelines	SPC update: This variation did not require European Commission approval. Otsuka Europe Development and Commercialisation submitted the application for a variation on 8 March 2018 and on 26 March 2018 the EMA confirmed the validity of the submission and issued a positive opinion. Otsuka Europe Development and Commercialisation sent the SPC update to Otsuka Europe and Otsuka UK on 28 March 2018 (the same day as the EMA notification), within the two days specified in EU-SOP-MA-002.v3, when this was in effect. However, the update was sent to an individual at Otsuka UK who was on leave rather than to the designated UK regulatory inbox. Otsuka UK sent the revised SPC to the eMC on 24 April 2018. Updated prescribing information:

	There was no requirement to revise the prescribing information following the SPC update. Promotional material: The promotional material for Abilify (see below) was not affected by the SPC update. Patient safety implications: There were no patient safety implications associated with this SPC update.

Material for Jinarc, Samsca, Abilify and Abilify Maintena certified from 1 January 2017

Review of material

Otsuka explained that Otsuka Europe produced and certified the material that it used and Otsuka UK produced and certified its material. Material relating to Abilify Maintena was currently certified by both Otsuka UK and Lundbeck.

Otsuka submitted that it had searched the Zinc Maps system for all materials relating to Jinarc, Samsca, Abilify or Abilify Maintena which would require incorporation of appropriate prescribing information certified from 1 January 2017 and used in the UK and/or with UK health professionals and as a result 1,407 job bags were reviewed. Of this material, Otsuka provided copies of all material certified from 1 January 2017 and active during a period commencing four weeks prior to the approval of a new prescribing information and certified up to four weeks after that prescribing information update, as well as material Otsuka had identified which was non-compliant with the requirements of the Code in one or more aspects. Only material certified active or certified withdrawn had been included. The amount of material provided therefore reflected 242 job bags.

The following was provided:

- Otsuka UK material for Jinarc and Samsca, active during a period commencing four weeks prior to the approval of a new prescribing information and certified up to four weeks after that prescribing information update, together with the associated certificates and withdrawal documentation;
- Otsuka UK material for Abilify and Abilify Maintena, active during a period commencing four weeks prior to the approval of a new prescribing information and certified up to four weeks after that prescribing information update, together with the associated certificates and withdrawal documentation;
- Otsuka Europe material for Jinarc and Abilify Maintena identified as non-compliant with the requirements of the Code in one or more aspects, together with the associated certificates (no items responsive to the criterion of 'active during a period commencing four weeks prior to the approval of a new prescribing information and certified up to four weeks after that prescribing information update'; no non-compliant material relating to Samsca were identified);
- Otsuka UK material identified for Jinarc which did not comply with the Code in one or more aspects, together with the associated certificates;

- Otsuka UK material identified for Samsca which did not comply with the Code in one or more aspects, together with the associated certificates;
- Material identified for Abilify Maintena which did not comply with the Code in one or more aspects together with the associated certificates.

Otsuka stated that it had identified seven Jinarc job bags which met the criteria set out above, relating to material issued by Otsuka Europe from 1 January 2017.

Otsuka stated that these seven job bags related to the updates of the Jinarc European website created in 2015. Whilst this website was not launched in the UK it permitted access by UK health professionals. These job bags did not include the latest version of the prescribing information, however, the current version of the SPC was included on the website. The situation had been addressed by deactivation of the website; its content and use were being reassessed.

Otsuka identified 440 Jinarc job bags, which met the criteria set out above, relating to material certified by Otsuka UK from 1 January 2017 (relevant material was provided).

Five of the Jinarc job bags did not include prescribing information (details and copies provided).

Jinarc was subject to a risk minimisation plan (RMP) approved as part of the marketing authorisation for the product and focussed on hepatic side-effects. The RMP included certain educational materials directed towards health professionals and patients, which must be approved by local regulatory authorities. This material was prepared and updated following a centralised procedure driven by Otsuka Europe and cascaded down to affiliates. In April 2018, the Otsuka UK medical team found that the January 2017 SPC update (addition of anuria as a contraindication) had not been included in certain educational items. The existing material complied with the previous SPC which, according to Otsuka, was considered appropriate by EMA in respect of anuria. Otsuka submitted that the EMA did not consider anuria as a new contraindication because the SPC already contained appropriate warning statements. Consequently, the company did not expedite update of the patient material. The following items did not include the anuria contraindication following the January 2017 SPC update:

Three Prescriber Check Lists, seven Patient Brochures and one other item (details were provided).

Further updates required as a result of the latest Jinarc SPC update in April 2018 (fluconazole interaction) had not been implemented (as of 20 June 2018).

The following items did not include the dose adjustment required as a result; five RMP training decks; two Health professional guides (details and copies of each item were provided).

The educational material required under the RMP was currently being updated and Otsuka expected to submit it to the MHRA for approval before the end of June 2018.

Otsuka submitted that between January 2017 and June 2018, there had only been one Jinarc SPC update that impacted the prescribing information and resulted in the withdrawal of a number of materials.

The withdrawal notice was not returned by one key account manager (KAM) by the due date of 7 April 2017. This KAM left Otsuka UK shortly afterwards.

One Samsca non-promotional job bag had been identified, which met the criteria set out above, issued by Otsuka Europe from 1 January 2017.

Fifty-two Samsca job bags had been identified which met the criteria set out above issued by Otsuka UK from 1 January 2017, none of which were missing prescribing information or did not include the latest version of prescribing information.

Between January 2017 and June 2018, there had only been one Samsca SPC change that impacted the prescribing information and resulted in withdrawal of materials.

Otsuka UK knew of this SPC change in November 2017. All materials with out-of-date prescribing information were immediately recalled and destroyed.

Otsuka identified 35 Abilify Maintena job bags issued by Otsuka Europe, which met the criteria set out above.

Two Abilify Maintena job bags did not include prescribing information (details and copies provided).

The company had identified 820 Abilify and Abilify Maintena job bags in both the Otsuka UK and Alliance UK sites, which met the criteria set out above, issued by Otsuka UK from 1 January 2017.

One out of 280 Abilify and Abilify Maintena promotional items during the relevant period did not incorporate prescribing information – a presentation given by a health professional at a meeting in March 2017. While prescribing information was included in the job bag at the review stage, it was inadvertently removed before final certification and therefore was not included in the final certified form. This job bag was certified by Otsuka UK only.

The May 2018 prescribing information was reviewed and certified by the Alliance and had been implemented across all 55 active materials.

<u>Overall summary: material relating to Jinarc, Samsca, Abilify and Abilify Maintena</u>

Otsuka stated that Otsuka Europe and Otsuka UK had carried out a detailed and thorough review of 1,407 items of material according to the criteria specified above. The deficiencies identified comprised a small number of the total and were disclosed with transparency.

Out of 1,407 job bags reviewed and certified by both Otsuka Europe and Otsuka UK for Jinarc, Samsca, Abilify and Abilify Maintena, the company had identified:

- 8 items with no prescribing information;
- 15 items where the latest prescribing information was not incorporated;
- 18 items where educational material had not yet been updated (subject to regulatory approval) following SPC updates.

Otsuka stated that these items represented a failure to meet acceptable standards. Prior to the complaint, Otsuka had carried out a detailed review and updated its procedures in order to ensure that such matters did not occur in future.

Otsuka stated that only one item (seven job bags) certified by Otsuka Europe was found to be deficient: the Jinarc European website. None of the deficiencies identified by Otsuka UK and listed above related to promotional material issued after December 2017 and all of the Otsuka UK promotional items subject to the deficiencies listed above had been withdrawn or corrected and recertified before the complaint was made.

Potential breaches of the Code

Clause 4.1 and 4.2:

Otsuka stated that the Code did not indicate the time for implementation of SPC updates or withdrawal of old material and it must, therefore, be reasonable for the substance of the particular update to influence such matters.

Prescribing information did not replace the SPC and, by definition, comprised a summary of the more important elements of the SPC. Therefore, while in some cases it would be obvious that an SPC update should result in revision to the prescribing information, in other cases that would be a question of judgement.

Otsuka submitted that none of the SPC updates to Jinarc, Samsca, Abilify or Abilify Maintena since January 2017 had involved an emerging safety issue or an urgent safety restriction and therefore the normal timelines were followed:

- In three of the six SPC updates listed above, no prescribing information change was needed and there was accordingly no basis for withdrawing existing promotional material;
- For three of the SPC updates (Jinarc (anuria contraindication), Samsca (7.5mg dosage form and incidence and management of RCHN) and Abilify/ Abilify Maintena (warning in relation to impulse control disorder)), it was decided that the prescribing information should be updated although this was completed on a routine basis in accordance with applicable SOPs:

    a) The prescribing information for Jinarc was revised 37 days after regulatory approval, consistent with the relevant SOP and a reasonable period in the context of the existing information about the need to secure urine output already present in the prescribing information before the update;
    b) The prescribing information for Samsca was updated on a non-urgent basis in circumstances where when the SPC was updated, there was no promotional activity being conducted, the prescribing information was revised before such activity was recommenced;
    c) The prescribing information for Abilify/Abilify Maintena was revised seven days after formal approval of the SPC update and no new promotional material was issued during the implementation period between regulatory approval and prescribing information revision.

Otsuka stated that the above demonstrated that Otsuka Europe and Otsuka UK had acted appropriately to update the prescribing information for their products, where necessary, following marketing authorisation variations in the context of all relevant updates since January 2017. Therefore, there had been no breach of Clause 4.1 or Clause 4.2 from failure to implement prescribing information updates.

However, a review of materials issued from 1 January 2017 indicated that, out of 1,407 items, 8 included no prescribing information and in 15 cases the incorrect prescribing information was included. Otsuka Europe and Otsuka UK recognised and regretted that these items were issued in breach of Clause 4.1 and Clause 4.2 of the Code. The associated errors were corrected before this complaint was made, all affected materials had been withdrawn or corrected and recertified and procedures had been strengthened to ensure that these deficiencies did not occur in future.

Clause 9.1:

Otsuka submitted that although all its current UK promotional material was compliant, it recognised that in the past its procedures had not been as robust as it had intended, with the result that communication had not always been effective. There had been some delays in implementing SPC updates, including notifying these to the eMC and so a programme of remediation was already advanced at the date of the complaint. Otsuka Europe and Otsuka UK had carried out an extensive programme of change and were in the process of effecting revised and stronger procedures to prevent such delays.

Furthermore, Otsuka had identified that the update of certain RMP material for Jinarc, which should have been updated following SPC updates (subject to regulatory approval), had not been affected. The company was currently updating such material and intended to submit to the MHRA for approval shortly.

The review had unfortunately shown a number of deficiencies in relation to implementation of updates to SPCs and subsequent incorporation of prescribing information. Otsuka noted that a detailed review of the safety database showed no evidence of an increase in product-related adverse events in relation to these updates, however, Otsuka could not completely exclude the potential risk to patients. Otsuka stated that it accepted a breach of Clause 9.1.

Clause 2:

Otsuka reiterated that promotional materials currently used by Otsuka Europe and Otsuka UK complied with the Code and they were urgently taking steps to update educational materials which formed part of the RMP for Jinarc.

Unfortunately, some historic materials had not been fully compliant and there had been some delays in implementing SPC changes on the eMC, in the RMP and in the prescribing information, as well as certain technical defects in certification arrangements. Otsuka recognised that these breaches of the Code were very serious. Its submission in relation to Clause 9 was also applicable here.

Well before the complaint was made, Otsuka had recognised that its procedures were not as robust as they needed to be and had substantially revised its processes to ensure that they had been strengthened and clarified. Otsuka was confident that the measures it had instituted and

was continuing to implement would ensure that its materials and other activities fully complied in the future.

In summary, Otsuka submitted that all of the Jinarc, Samsca and Abilify prescribing information and promotional material currently being used by Otsuka Europe and Otsuka UK was up-to-date, reflected the current SPC and otherwise complied with the Code. Nevertheless, the company recognised that its procedures in the past had not been as robust as it would have wished. This had resulted in delays in notifying SPC changes to the eMC and the deficiencies in relation to the material identified during its review, as set out above. The company had taken steps to remedy the situation from early 2018, substantially before the complaint was made, and its corrective measures had been implemented or were now advanced.

PANEL RULING

The Panel noted that whilst Otsuka UK was not a member of the ABPI, Otsuka Europe was a member of the ABPI and, as such, it was obliged to comply with the Code. Otsuka Europe was thus responsible under the Code for any acts and omissions of Otsuka UK that fell within the scope of the Code. The Panel noted that Otsuka was also a member of EFPIA and IFPMA.

The Panel noted that Otsuka Europe was the marketing authorisation holder for Jinarc, Samsca and Abilify which were supplied in the UK by Otsuka UK. Otsuka Europe was also the marketing authorisation holder for Abilify Maintena which was supplied in the UK by Otsuka UK and Lundbeck under a co-promotion agreement. It appeared from the various standard operating procedures that Otsuka Europe Development and Commercialisation was responsible for notifying Otsuka Europe of any changes to the SPCs. The Panel considered that it was unclear whether it was Otsuka Europe or Otsuka Europe Commercialisation and Development that was ultimately responsible for communicating the SPC and PIL changes to Otsuka UK; SOP EU-SOP-MA-002 v3 placed responsibility upon Otsuka Europe to notify affiliates of such changes whilst SOP EU-SOP-RA-002 v5 described notification by Otsuka Europe Commercialisation and Development. Historically, affiliates were then responsible for implementing the changes including updating the prescribing information. The Panel noted that a guidance document sent out on 7 June 2018 stated that summary/abbreviated prescribing information for promotional materials would, going forward, be provided by Otsuka Europe (previously developed separately by affiliates). Otsuka UK was, and remained, responsible for updating the eMC. The Panel noted Otsuka's submission that Otsuka UK and Otsuka Europe each produced and certified the material it used.

The Panel noted that the complainant referred to SPC updates from 2017 and thus the companies were asked to respond in relation to updates since 1 January 2017.

Case AUTH/3042/6/18 – Otsuka UK

1 Jinarc

A Addition of anuria as a contraindication to Section 4.3 of the SPC

The Panel noted that, according to Otsuka, the Committee for Medicinal Products for Human use (CHMP) issued a positive opinion on 15 September 2016 recommending the inclusion of anuria as a new contraindication. The Panel noted Otsuka's submission that the European Medicines Agency (EMA) advised Otsuka Europe Development and Commercialisation by

telephone on 6 January 2017 that it did not consider the update to be a new contraindication, but simply new wording emphasising the existing safety information and advised Otsuka that it should implement the update immediately without waiting for Commission approval. Otsuka Europe Development and Commercialisation communicated the update to Otsuka Europe and Otsuka UK on 9 January 2017, which Otsuka treated as the start date of formal approval for implementation of the update. Otsuka UK implemented the SPC update but did not send the revised SPC to the eMC until 3 February 2017. The Panel considered that the delay in sending the updated SPC to the eMC meant that Otsuka UK had failed to maintain high standards and a breach of Clause 9.1 was ruled.

The Panel noted that the general principle was that prescribing information (defined by Clause 4.2) must be up-to-date and must comply with Clauses 4.1 and 4.2 of the Code which included providing a succinct statement of, *inter alia*, contra-indications giving in an abbreviated form the relevant information in the SPC. The prescribing information must be consistent with the SPC for the medicine. The Panel noted that a company could chose to provide the SPC as part of the prescribing information; in such circumstances the SPC provided must be the most current one.

Otsuka UK prepared updated prescribing information on 17 February 2017. The Panel noted Otsuka's submission that while the SPC update represented the addition of a contraindication, the EMA viewed the change as 'minor'. The Panel disagreed with Otsuka's submission that the SPC update was not regarded as constituting important safety information requiring adoption of the accelerated prescribing information amendment under the relevant SOP because: Jinarc was only indicated in patients with stages 1-3 chronic kidney disease (who would not be anuric); the SPC had previously included a recommendation under 'precautions and warnings' that urinary output should be secured; and the 'posology' section previously included a recommendation to discontinue use if renal insufficiency progressed to chronic kidney disease stage 5, which could result in anuria. In the Panel's view, this did not preclude the need to update the contraindications section of the prescribing information to include anuria.

The Panel noted Otsuka's submission that new promotional material incorporating the revised prescribing information was issued from 1 March 2017. However, it was of concern that existing promotional material which pre-dated the SPC update was only withdrawn on 29 March 2017 as a routine withdrawal, rather than to ensure compliance with the Code after the SPC update. The Panel noted that Clause 4.2 listed the components of prescribing information which had to be provided including, *inter alia*, contraindications relevant to the promoted indication. Failure to provide the required information in the prescribing information would be a breach of Clause 4.1. The Panel considered that all promotional material that was not withdrawn until 29 March and contained prescribing information that omitted the anuria contraindication and was, therefore, inconsistent with the SPC current at that time, was not up-to-date and was therefore in breach of Clause 4.1. The Panel considered that the delay in updating the prescribing information and withdrawing material with out-of-date prescribing information meant that Otsuka UK had failed to maintain high standards and a breach of Clause 9.1 was ruled.

The Panel queried whether Otsuka's standard timelines for implementation of changes to the prescribing information of six months after approval, as referred to in OPUK-SOP-MA-010 version 6, was appropriate.

The Panel noted Otsuka's submission that in April 2018, Otsuka UK discovered that anuria as a contraindication had not been included in certain educational materials required under a risk

minimisation plan (RMP). The Panel was concerned to note that the educational material implementing the RMP had still not been updated and submitted to the MHRA for approval at the time of Otsuka's response to this complaint (June 2018). The Panel considered that Otsuka UK had failed to maintain high standards by not promptly updating educational material required under the RMP and a breach of Clause 9.1 was ruled. The Panel considered that such failures had potential patient safety implications and noted its comments on Clause 2 and ruling on this matter at point 5 below.

B Inclusion of clinical trial results from the post-authorisation study in Section 5.1 of the SPC

The Panel noted that the CHMP issued a positive opinion on 6 July 2017 to update Section 5.1 of the Jinarc SPC to include clinical trial results from the post-authorisation study, an extension to the TEMPO trial, which evaluated the effects of tolvaptan on, *inter alia*, safety. Otsuka Europe Development and Commercialisation communicated the SPC update to Otsuka Europe and Otsuka UK the same day. The Panel noted Otsuka's submission that the communication was, however, not received by Otsuka UK until November 2017 and Otsuka sent the revised SPC to the eMC on 29 November 2017. The reason for this delay was unclear; Otsuka made no submission in this regard. The Panel considered that the substantial and unexplained delay in Otsuka UK implementing the SPC change and updating the eMC meant that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted the content of prescribing information as listed in Clause 4.2 and that some changes to an SPC might not need to be reflected in the prescribing information. The Panel noted Otsuka's view that this SPC revision had not necessitated a change to the prescribing information. The complainant bore the burden of proof and, in the Panel's view, he/she had not established that the SPC update necessitated a change to the prescribing information. The Panel therefore ruled no breach of Clause 4.1.

C Addition of drug interaction (fluconazole) to Section 4.5 of the SPC

The Panel noted that whilst fluconazole had been listed as a moderate CYP3A inhibitor in Section 4.5 of the Jinarc SPC since marketing authorisation was granted in May 2015, the CHMP issued a positive opinion on 12 April 2018 to include additional information regarding the co-administration of tolvaptan and fluconazole and the 200% increase in tolvaptan area under time-concentration curve (AUC) and the 80% increase in the maximum observed plasma concentration (C_{max}). Otsuka Europe Development and Commercialisation communicated the SPC change to Otsuka Europe and Otsuka UK on 16 April 2018. Otsuka UK implemented the update and sent the revised SPC to eMC on 25 April 2018. The Panel did not consider that Otsuka UK had failed to maintain high standards in this regard and no breach of Clause 9.1 was ruled.

The Panel noted its comments above that some changes to an SPC might not need to be reflected in the prescribing information. The Panel noted Otsuka UK's view that this SPC revision had not necessitated a change to the prescribing information as information regarding CYP3A inhibitors was already included in the prescribing information. The Panel noted that fluconazole was listed as a moderate CYP3A inhibitor in the SPC. The complainant bore the burden of proof and, in the Panel's view, he/she had not established that the SPC update necessitated a change to the prescribing information. The Panel therefore ruled no breach of Clause 4.1.

The Panel noted Otsuka's submission that, upon review of its materials, a number of Jinarc RMP training materials and health professional guides did not contain the dose adjustment required as a result of the Jinarc SPC update in April 2018 in relation to the interaction with fluconazole. The Panel noted its comments above. Section 4.5 of the SPC referred to dose reduction of Jinarc when patients were taking moderate or strong CYP3A inhibitors and stated that such patients should be managed cautiously. Section 4.2 of the SPC gave the recommended Jinarc dose reductions for those patients. The Panel further noted, with concern, that on its examination of the SPCs, the Jinarc dose reduction recommendation for patients taking moderate CYP3A inhibitors, including fluconazole, appeared to have been in the SPC since the grant of the marketing authorisation in May 2015, rather than April 2018 as implied by Otsuka, and thus the company's submission on this point was incorrect. The Panel was concerned to note Otsuka's submission that the RMP material had yet to be updated and submitted to the MHRA at the time of Otsuka's response to this complaint and considered that Otsuka had failed to maintain high standards by not promptly updating educational material required under the RMP. A breach of Clause 9.1 was ruled. The Panel considered that such failures had potential patient safety implications and noted its comments on Clause 2 and ruling on this matter at point 5 below.

2 Samsca

Extension application and updates to undesirable effects, rapid correction of hyponatraemia (RCHN) and posology and method of administration

The Panel noted Otsuka's submission that the European Commission decision to update the Samsca SPC to include the 7.5mg dosage form and update the undesirable effects, posology and method of administration was adopted on 18 September 2017. The update included the change in incidence of an adverse event, rapid correction of hyponatraemia (RCHN) from common to very common and a recommendation to use a lower dose in patients susceptible to RCHN.

Otsuka Europe Development and Commercialisation communicated the update to Otsuka Europe and Otsuka UK on 20 September 2017. The Panel noted Otsuka's submission that the notification was sent to the incorrect person at Otsuka UK and was therefore not received. The communication was re-sent to Otsuka UK on 21 November 2017. Otsuka UK implemented the SPC update but did not send the revised SPC to the eMC until 8 January 2018. The Panel considered that the delay in implementing this SPC update and sending it to the eMC meant that high standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel noted the nature of the SPC update and considered that such failures had potential patient safety implications. The Panel noted its comments on Clause 2 and ruling on this matter at point 5 below.

The Panel was concerned to note Otsuka's submission that existing promotional material, which pre-dated the SPC update, was only withdrawn on 4 December 2017. The Panel noted, however, Otsuka's submission that no promotional activity took place between the end of September 2017 and February 2018 and so, in Otsuka's view, there was no requirement to revise the prescribing information when the SPC was updated. The Panel queried why, if the material was not being used, it was not withdrawn sooner. The Panel noted that Otsuka had not commented on any applicable online promotional materials such as those available on websites. The Panel noted Otsuka's submission that the prescribing information was ultimately

revised on 9 January 2018, before promotion started in February 2018 and promotional material incorporating changes following the SPC update was first issued on 18 March 2018.

Whilst the Panel had concerns, it noted that there was no evidence before it that material with out-of-date prescribing information had been distributed or was available online. The complainant had provided insufficient evidence to discharge the burden of proof on the balance of probabilities; no breach of Clause 4.1 was ruled. The Panel considered, however, that failure to withdraw such material to ensure it could not be used meant that Otsuka had failed to maintain high standards and a breach of Clause 9.1 was ruled.

3 Abilify and Abilify Maintena

A Addition of specific warnings

The Panel noted Otsuka's submission that the CHMP issued a positive opinion on 26 October 2017 and recommended approval of an SPC update to add specific warnings related to impulse control disorder, binge eating, compulsive shopping and poriomania.

The Panel noted Otsuka's submission that the date the linguistic review ended (4 December 2017) was the SPC update implementation date. The Panel further noted Otsuka's submission that Otsuka Europe Development and Commercialisation communicated the SPC update to Otsuka Europe and Otsuka UK on 7 December 2017. Lundbeck, which co-promoted Abilify Maintena in the UK, was notified on 11 December. According to Otsuka, the revised SPCs for the various Abilify formulations were sent to the eMC between 25 January 2018 and 5 February 2018. The Panel considered that the delay in updating the eMC with the SPC change, which included additional information in Section 4.4 (special warnings and precautions for use) and the addition of new adverse drug reactions to Section 4.8 meant that high standards had not been maintained and a breach of Clause 9.1 was ruled. The Panel considered that such failures had potential patient safety implications and noted its comments on Clause 2 and ruling on this matter at point 5 below.

The Panel was concerned to note Otsuka's submission that this SPC update would generally have prompted update of promotional material in line with standard timelines under EU-SOP-MA-002.03 (within 6 months of formal approval and not later than implementation of updated PIL in finished product packs). It appeared that the revision of the prescribing information was carried out in accordance with accelerated timelines only because review of the prescribing information indicated that improvement was needed irrespective of the SPC update. The nature of such further required improvement was not stated.

The Panel queried whether Otsuka's standard timelines for implementation of changes to the prescribing information of six months after approval, as referred to in EU-SOP-MA-002.03 and OPUK-SOP-MA-010 v6, was appropriate. The Panel noted that the general principle was that prescribing information (defined by Clause 4.2) must be up-to-date, must comply with Clause 4.1 and 4.2 of the Code and must be consistent with the SPC.

The Panel noted, however, Otsuka's submission that existing promotional material, which pre-dated the SPC update, was withdrawn on 28 November 2017. No promotional material was issued between 4 December 2017 (date SPC update approved) and 11 December 2017 (date prescribing information revised). The Panel, therefore, ruled no breach of Clause 4.1.

B Abilify oral solution – Section 6.1 change of flavour

The Panel noted that there was an update to Section 6.1 of the Abilify oral solution SPC regarding a change of flavour. The Panel noted Otsuka's submission that the update did not require European Commission approval; EMA confirmed the validity of the submission and issued a positive opinion on 26 March 2018.

Otsuka Europe Development and Commercialisation communicated the SPC update to Otsuka Europe and Otsuka UK on 28 March. The update was, however, sent to an individual Otsuka UK employee who was on annual leave at the time rather than to the designated UK regulatory inbox.

Otsuka UK sent the revised SPC to the eMC on 24 April 2018. The Panel was particularly concerned to note that this delay occurred despite Otsuka's submission that a task force to implement corrective and preventative measures was put in place in February 2018, after an Otsuka UK employee had raised concerns about the company process in November 2017. The Panel considered that high standards had not been maintained and ruled a breach of Clause 9.1.

The Panel noted Otsuka's submission that there was no requirement to revise the prescribing information and no promotional material was affected due to this SPC change. The Panel noted that the complainant bore the burden of proof and had not established that the SPC update necessitated a change to the prescribing information. No breach of Clause 4.1 was ruled.

4 Otsuka UK – Jinarc, Samsca, Abilify and Abilify Maintena materials certified from 1 January 2017

The Panel noted Otsuka's submission that it had reviewed Otsuka UK Jinarc, Samsca, Abilify and Abilify Maintena materials certified from 1 January 2017 and had identified five Abilify Maintena and three Jinarc promotional materials that did not contain the latest version of prescribing information and one Abilify Maintena and five Jinarc promotional materials that were missing prescribing information. The Panel noted that Otsuka might have been referring to what it considered to be the latest version of Otsuka approved prescribing information; given its ruling above the Panel considered that what Otsuka considered to be the latest version of prescribing information might not have met the requirements of the Code. The Panel further queried whether the search criteria adopted by Otsuka captured all affected materials in scope of the complaint. In relation to the materials that Otsuka submitted did not contain the latest version of prescribing information the Panel considered that in relation to Jinarc its ruling above at Point 1A appeared to cover this matter and it made no further ruling. In relation to each of the five Abilify Maintena materials that Otsuka submitted did not contain the latest version of prescribing information the Panel ruled a breach of Clause 4.1. A breach of Clause 4.1 was ruled in relation to each of the six materials noted above that Otsuka submitted were missing prescribing information. High standards had not been maintained and a breach of Clause 9.1 was ruled. The Panel considered that such failures had potential patient safety implications and noted its comments on Clause 2 and ruling on this matter at point 5 below.

5 Clause 2

The Panel noted that it was crucial that health professionals and others could rely upon the industry for up-to-date and accurate information about their medicines. The Panel was

concerned to note Otsuka UK's failures to implement SPC changes and to promptly: update the eMC website; update prescribing information; withdraw materials including promotional material with out-of-date prescribing information; and update and submit material required under the RMP to the MHRA. The Panel noted its comments above at Jinarc (Points A, C), Samsca, (Point A), Abilify/Abilify Maintena (Point A) and in relation to materials at Point 4 above, and that there were potential patient safety implications as a result of such failures.

The Panel was particularly concerned about the volume of educational material required under the Jinarc RMP that had not been updated and submitted to the MHRA for approval at the time of Otsuka's response to this complaint (June 2018); this included eleven materials that did not include the anuria contraindication following an SPC update in January 2017 and seven materials that did not include the dose adjustment that Otsuka stated was required following the fluconazole interaction SPC update in April 2018. The latter was of particular concern given that the relevant recommended Jinarc dose reduction for patients taking moderate CYP3A inhibitors including fluconazole appeared, contrary to Otsuka's submission, to have been in the SPC since May 2015, when Jinarc was granted its marketing authorization. The Panel was concerned that Otsuka only appeared to have become aware of these omissions when responding to this complaint and was further concerned that its submission about when the Jinarc dose adjustment for patients taking fluconazole first appeared in the SPC was incorrect. It was important, and fundamental to self-regulation, that companies submitted accurate information when responding to complaints.

The Panel considered that such failures brought discredit upon, and reduced confidence in, the pharmaceutical industry. 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 new information, the omission of which could potentially impact patient safety. A breach of Clause 2 was ruled.

The Panel noted that Otsuka was trying to address the issues in question. Despite such efforts, it was clear that governance issues remained; for instance, the late provision of the revised Abilify SPC to the eMC on 24 April 2018, and the omissions in and failure to promptly update Jinarc RMP material. The Panel noted the breadth and depth of the company's compliance difficulties. In the Panel's view, it was likely that the compliance issues went beyond matters that arose from the narrow set of materials identified by Otsuka in response to this complaint and beyond matters raised by the complainant. For instance, relevant materials certified before 1 January 2017 may have required updated prescribing information. The Panel noted that its brief review of the company's SOPs raised further concerns in relation to governance. In addition, the Panel noted that some Jinarc RMP materials appeared to contain incorrect information regarding interaction with strong CYP3A inhibitors (an example of which was ketoconazole). In places, ketoconazole was incorrectly referred to as a CYP3A substrate rather than as a CYP3A inhibitor and the information appeared to be inconsistent with the SPC. Otsuka would be advised to carefully review the information in all its RMP materials to ensure it is consistent with the SPC. The Panel considered that its concerns in relation to this case and broader concerns about the company's governance warranted reporting Otsuka UK to the Appeal Board under Paragraph 8.2 of the Constitution and Procedure for the Appeal Board to consider in relation to Paragraph 11.3 of the Constitution and Procedure.

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Case AUTH/3041/6/18 Otsuka Europe

The Panel noted that it was unclear from Otsuka's submission what actions Otsuka Europe had taken when notified of each SPC update by Otsuka Europe Development and Commercialisation. It was of concern that no information was given about withdrawal of materials by Otsuka Europe. The Panel noted that it appeared from Otsuka's response that Otsuka UK was responsible for notifying eMC.

The Panel noted Otsuka's submission that Otsuka Europe produced and certified the materials it used. The Panel noted Otsuka's submission that upon review of all Jinarc, Samsca, Abilify and Abilify Maintena materials certified from 1 January 2017 that required prescribing information and were issued by Otsuka Europe and used in the UK and/or with UK health professionals it identified 7 Jinarc promotional materials issued by Otsuka Europe related to a website that did not contain the latest version of the prescribing information. The Panel ruled breaches of Clause 4.1 in relation to each of these materials.

The Panel noted Otsuka's submission that it had not identified any Samsca materials issued by Otsuka Europe since 1 January 2017 that did not include the latest version of the prescribing information. The Panel noted the complainant bore the burden of proof and had not established that any Samsca material issued by Otsuka Europe since 1 January 2017 contained out-of-date prescribing information. The Panel thus ruled no breach of Clause 4.1.

The Panel noted Otsuka's submission that it had not identified any Abilify or Abilify Maintena materials issued by Otsuka Europe that did not contain the latest version of prescribing information, however, it had identified two Abilify Maintena materials that were missing prescribing information and a breach of Clause 4.1 was ruled in relation to each.

In the Panel's view, and noting its rulings above, governance of materials at Otsuka Europe had fallen below acceptable standards. The Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel noted instances where Otsuka UK had not received prompt communication regarding an SPC update because the notification was sent to the incorrect person or to an individual who was on leave rather than to a designated UK regulatory inbox. The Panel noted its comments and rulings above in Case AUTH/3042/6/18. The Panel also considered that certain comments above at Case AUTH/3042/6/18 were relevant in relation to poor governance by Otsuka Europe. The Panel considered that the failures had potential patient safety implications as noted in Case AUTH/3042/6/18. It was crucial that health professionals and others could rely completely upon the industry for up-to-date and accurate information about their medicines. The Panel considered on balance that the cumulative effect of its rulings and comments above brought discredit upon and reduced confidence in the pharmaceutical industry and warranted a ruling of a breach of Clause 2 and ruled accordingly.

Good governance of the process for notifying affiliates of SPC and PIL updates was critical and had potential patient safety implications. Furthermore, some SPC updates might require an update to the prescribing information and the subsequent withdrawal of existing promotional material. The Panel considered that, in general, and noting its comments and rulings above, Otsuka Europe's overall governance in relation to its processes and materials above appeared to be poor. The Panel noted Otsuka's submission that processes fell short of expected high standards and the time for remediation was too long. Otsuka submitted that it had taken steps to address the issues including that from June 2018 affiliates would be asked to confirm

implementation of SPC and PIL updates to facilitate tracking and the prescribing information would now be provided by Otsuka Europe rather than developed separately by the affiliates. The Panel was concerned that confirmation of implementation of SPC and PIL updates was apparently not recorded prior to June 2018.

Although it appeared from its submission that Otsuka Europe was trying to address some of the issues in question, the Panel considered that its concerns in relation to this case warranted reporting Otsuka Europe to the Appeal Board under Paragraph 8.2 of the Constitution and Procedure for the Appeal Board to consider in relation to Paragraph 11.3 of the Constitution and Procedure.

The Panel further noted that Otsuka raised Clause 14.1 in its response with regard to a number of Abilify Maintena materials that had been certified by one company on behalf of both Otsuka and Lundbeck when the PMCPA and MHRA had not been notified of such arrangements in advance. The Panel noted that an allegation had not been made in this regard and it could therefore make no ruling.

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Otsuka Europe and Otsuka UK

During the consideration of Cases AUTH/3041/6/18 and AUTH/3042/6/18 the Panel was concerned to note that Otsuka SOPs allowed up to six months to update promotional material when the company considered the SPC change a 'standard' update and 10 business days to update promotional materials when there was an urgent safety update. The Panel noted that it was a requirement that promotional material was, *inter alia*, up-to-date and must be consistent with the SPC.

COMMENTS FROM OTSUKA EUROPE AND OTSUKA UK ON THE REPORT FROM THE PANEL

Otsuka Europe

Otsuka Europe provided the requisite undertaking and assurance in respect of the Panel's rulings of breaches of Clauses 2, 4.1 and 9.1 in Case AUTH/3041/6/18.

Otsuka Europe regretted the actions and inactions that had brought it to this point and was hopeful that it would have the opportunity to demonstrate its commitment to improve. Otsuka Europe stated that since June 2018, it had embarked on an ambitious continuous improvement programme, some of which had already been communicated in its response to Case AUTH/3123/11/18. Otsuka Europe acknowledged that its progress had been slower than anticipated, and that the additional issues raised to the PMCPA in January 2019 indicated it had a long road ahead.

The company submitted, however, that it was important to recognise that compliance programmes were not rebuilt over a short time; they required dedicated effort over the long term. To that end, Otsuka Europe would:

- continue to commit resources to face-to-face interactive training to enhance employees' understanding and would continue to improve its compliance training programme;

- continue to strengthen European regional and Otsuka Europe-specific procedures, including the SOPs which described the process to communicate SPC changes;
- improve its monitoring capabilities once training was completed and SOPs were embedded in order to measure compliance and ensure continuous improvement;
- enhance its ability to correctly identify prescribing information versions through a central repository;
- invest in new tools to help certify materials and events, as well as manage incident reporting and investigations and
- recruit an experienced compliance professional to join an already expanded compliance team and assist Otsuka Europe in implementing an enhanced compliance programme.

Otsuka Europe stated that both Otsuka Europe and Otsuka UK were one company and were committed to self-regulation and high ethical standards. Otsuka Europe recognized the severity of the issues and accepted the Panel's rulings. Otsuka Europe stated it must, and would, continue to do better.

Otsuka UK

Otsuka UK accepted the Panel's rulings of breaches of Clauses 2, 4.1 and 9.1 in Case AUTH/3042/6/18 and provided the requisite undertaking and assurance.

Otsuka UK stated that since May 2017, it had been making progress to strengthen the processes and governance within the affiliate. This had included the restructuring of commercial and medical teams, recruiting a new senior leadership team and updating numerous SOPs. Otsuka UK looked forward to sharing its progress in this area with the Appeal Board.

Otsuka UK submitted that it took patient safety extremely seriously and it deeply regretted the historical failings in this area. Otsuka UK was fully committed to ensuring that this did not happen again.

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At the consideration of the three reports at the same Appeal Board meeting, Otsuka made one presentation in relation to Case AUTH/3041/6/18 (Otsuka Europe) and Case AUTH/3042/6/18 (Otsuka UK) which also covered Case AUTH/3123/11/18. The following comments were made in relation to all three cases.

The company representatives from both Otsuka UK and Europe accepted accountability and agreed that Otsuka had not met the required standards and it had let down patients, customers, partners, employees and the industry. Otsuka noted that the speed of remediation of these issues had not been fast enough.

Otsuka noted that it was making fundamental changes in relation to people/culture, process and structure/governance. Moving forward, there would be a continuous improvement programme (CORE) across Otsuka which was being led by the managing director from Otsuka UK. There was a new head of compliance and medical at Otsuka Europe. The senior leadership team at Otsuka UK had been in place since November 2017.

In relation to the Jinarc Risk Management Plan (RMP), Otsuka submitted that materials at launch contained an error and there had been no consistent update of RMP materials since launch in 2015. There was no oversight of this material and no process for its update. Furthermore, communication of RMP updates was not consistent. Otsuka submitted that the process for the update of RMP materials in relation to SPC updates would become effective at the end of March 2019 and that all current materials were approved by the MHRA in November 2018 and up-to-date. Otsuka UK would update RMP materials should a change in SPC necessitate a safety-related change.

An internal audit carried out by an external consultant was due to report shortly. Headquarters in Japan had been kept up-to-date throughout the process.

Individually and collectively Otsuka committed to conducting its business with integrity and transparency, to the highest ethical standards and to place patients and customers at the heart of its business. Otsuka anticipated that the Appeal Board would require an audit of its procedures and it looked forward to demonstrating its improvements.

APPEAL BOARD CONSIDERATION OF THE REPORT FROM THE PANEL

The Appeal Board noted the Panel's comments and rulings of breaches of Clauses 2, 4.1 and 9.1 of the Code in Cases AUTH/3041/6/18 and AUTH/3042/6/18, including its decision to report Otsuka Europe and Otsuka UK to the Appeal Board. The Appeal Board noted that Otsuka Europe and Otsuka UK had provided detailed information about their compliance difficulties and they had apologised.

The Appeal Board noted the timelines provided showing European remediation to date from March 2018. It appeared from questioning the company representatives that little activity had taken place following the internal audit in September 2016 and when the issue was raised internally in November 2017. It was only after the complaint was made to the PMCPA in June 2018 that action was taken. This raised concerns about how seriously the company took the issue, its impact on patient safety and the culture at Otsuka. The company representatives stated that the delay was due to a lack of understanding of the seriousness and importance of the process. There was a lack of communication across the company. Senior leaders had apologised to employees. Speak-up processes had been introduced and more was shared about reporting incidents.

The Appeal Board noted the company's submission that it recently had another internal audit of its end-to-end processes and it was awaiting that report. The company representatives referred to the CORE programme which started in February 2019 led by the UK. The CORE programme had 4 elements; culture and compliance, one organisation, ready for audit and everybody was responsible for compliance. The company representatives also referred briefly to other issues identified mentioning meetings and congresses. These would be prioritised. Otsuka UK referred to a new meetings process.

The Appeal Board was very concerned that an overall failure of governance in relation to Otsuka Europe and Otsuka UK's processes in implementing SPC changes, updating prescribing information, updating and withdrawing promotional materials, and the update and submission to the MHRA of its risk minimisation materials in a timely manner had potential patient safety implications. It was crucial that health professionals and others could rely completely upon the industry for up-to-date and accurate information about its medicines. The

Appeal Board noted Otsuka UK and Otsuka Europe's submission that they were now putting systems and processes in place to address these issues. The Appeal Board noted the scale of the task but queried whether this was being done sufficiently quickly given the seriousness of the matter.

The Appeal Board decided that in accordance with Paragraph 11.3 of the Constitution and Procedure, Otsuka Europe and Otsuka UK should be publicly reprimanded for the failures to implement SPC changes and update impacted materials in a timely manner which had potential to impact patient safety. The Appeal Board also decided to require audits of Otsuka Europe and Otsuka UKs' procedures in relation to the Code in Cases AUTH/3041/6/18 and AUTH/3042/6/18. These audits should take place by mid July 2019. The audits would take place at the same time as that required in Case AUTH/3123/11/18. On receipt of the report of the audits, the Appeal Board would consider whether further sanctions were necessary.

APPEAL BOARD FURTHER CONSIDERATION

On receipt of the report for the July 2019 audits the Appeal Board was very concerned to note the extent of the companies' failings including that there was a systemic lack of governance shown by the failure to take action in these cases. Leadership and communication needed to be improved urgently. The governance from Japan to Europe and from Europe to UK needed huge improvement. There appeared to be longstanding failures in this regard, particularly in relation to holding senior individuals to account.

The Appeal Board noted that the report of the audits highlighted a number of concerns including that existing senior staff needed to improve their knowledge and leadership on compliance matters, engage with and ensure that all staff understood its importance. Staff should be helped and encouraged to improve their skills in relation to matters covered by the Code. Significant commitment was required to address the issues.

The Appeal Board noted from the report of the audits that Otsuka Europe had not provided accurate information about the training of the SOPs to the Appeal Board in March 2019 when the reports from the Panel were considered. The Appeal Board noted that self-regulation relied upon, *inter alia*, the provision of complete and accurate information from pharmaceutical companies. The Appeal Board decided that in accordance with Paragraph 11.3 of the Constitution and Procedure, Otsuka Europe should be publicly reprimanded for providing inaccurate information to the Appeal Board.

The Appeal Board noted Otsuka's compliance plan and decided that Otsuka should provide a detailed written account of its progress by the end of November 2019. It was vital that swift comprehensive action was taken and noting the failure to take appropriate action over a long period of time, the Appeal Board considered that given the exceptional circumstances of this matter, including the scale and seriousness of the difficulties at Otsuka, it would be helpful if Otsuka representatives attended the December 2019 meeting of the Appeal Board to discuss the progress and future plans. The Appeal Board noted that both Otsuka Europe and Otsuka UK had set themselves a number of compliance objectives and considered that sufficient time would be needed for these to be completed in order for any meaningful progress to be assessed. The Appeal Board decided that both Otsuka Europe and Otsuka UK should be re-audited in early 2020. At its meeting in December the Appeal Board would decide the timing of the re-audits and on receipt of the report for the re-audits it would decide whether further sanctions were necessary.

APPEAL BOARD FURTHER CONSIDERATION

At its meeting in December 2019 representatives from Otsuka Europe and Otsuka UK attended to discuss the progress and future plans. The companies welcomed the opportunity to provide the Appeal Board and PMCPA with a written account of the activities conducted and progress made since receipt of the report of the audits. The Appeal Board noted that whilst there was a lot of work to be done, a number of activities and actions were completed, planned and/or in process. On the information before it the Appeal Board decided that the re-audits should take place in April 2020 at which point it expected substantial improvements. On receipt of the report for the re-audits it would decide whether further sanctions were necessary.

APPEAL BOARD FURTHER CONSIDERATION

On receipt of the report for the April 2020 re-audits the Appeal Board noted the difficulties of conducting audits remotely and that there was little new activity due to the continuation of the 'pencils down'/'deprioritisation' policies. The Appeal Board considered that there had been some progress and it appeared that things were now heading in the right direction. There had been changes with new staff and new members of the Otsuka Board as well as additional resource for compliance and compliance objectives had been introduced. Key senior staff still needed to continue to develop their leadership on compliance. The Appeal Board noted that whilst most staff understood the reasons for the re-audits; it was concerned that some staff still did not. Otsuka UK and Otsuka Europe needed to continue to improve working relationships, including in and between the medical departments. It appeared that communication with Japan had improved. There was to be a staff survey in late 2020.

The Appeal Board noted that further improvement was required, the report of the re-audits highlighted a number of areas on which to focus.

The Appeal Board decided that Otsuka UK and Otsuka Europe should be re-audited in April 2021 at which point it also expected the companies to demonstrate continued progress and improvement. On receipt of the of the report for the re-audits the Appeal Board would decide whether further sanctions were necessary.

APPEAL BOARD FURTHER CONSIDERATION

On receipt of the report for the April 2021 re-audits the Appeal Board the Appeal Board considered that there had been some further progress and it appeared that matters were continuing to head in the right direction. However, the Appeal Board considered that the pace of improvement needed to accelerate. Otsuka UK and Otsuka Europe needed to continue to improve working relationships, including in and between the medical departments. Senior staff needed to work together to continue to improve their knowledge and leadership on compliance. There was currently no permanent medical lead for Otsuka Europe and there had been some restructuring. The Appeal Board considered it important that a medical lead for Otsuka Europe was appointed.

The Appeal Board noted that further improvement was required, the report of the re-audits highlighted a number of areas on which to focus.

The Appeal Board decided that Otsuka UK and Otsuka Europe should be re-audited in December 2021/January 2022 at which point it expected the companies to demonstrate continued progress and embedded improvement. On receipt of the report for the re-audits the Appeal Board would decide whether further sanctions were necessary.

APPEAL BOARD FURTHER CONSIDERATION

On receipt of the report for the January 2022 re-audits the Appeal Board noted that Otsuka had continued to build on the improvements described in the report of the 27 and 28 April 2021 re-audits. It was important that progress on company culture continued such that there was a team approach both within each company and between each company.

The Appeal Board noted that the report of the January 2022 re-audits still highlighted work to be done and it was important that these were addressed.

The Appeal Board considered that from the report of the January 2022 re-audits it appeared that there had been further progress. The Appeal Board was concerned that it had taken 4 audits/re-audits to get to this stage.

The Appeal Board noted that Otsuka had a compliance CORE tracker to address recommendations from the re-audits. On the basis that this work was completed, the progress shown to date was continued and commitment to compliance was maintained, the Appeal Board decided that no further action was required.

Complaint received	**1 June 2018**
Undertakings received	**Case AUTH/3041/6/18 – 7 February 2019** **Case AUTH/3042/6/18 – 8 February 2019**
Appeal Board consideration	**13 March, 18 September 2019, 11 December 2019, 17 September 2020, 22 July 2021, 10 March 2022**
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