CASES AUTH/3219/6/19 and AUTH/3220/6/19

VOLUNTARY ADMISSIONS BY OTSUKA EUROPE AND OTSUKA UK

Errors and omissions in prescribing information

Otsuka Pharmaceuticals Europe Ltd and Otsuka Pharmaceuticals UK Ltd admitted breaches of the Code in that there were errors and omissions in the current prescribing information for Abilify (aripiprazole), Abilify Maintena (aripiprazole), Jinarc (tolvaptan) and Samsca (tolvaptan). Otsuka Europe stated that given the centralised process that it followed, similar errors and omissions were likely to be seen in the prescribing information of the European affiliates and had been seen in the prescribing information used in the UK which was why the voluntary admission was made jointly between Otsuka Europe and Otsuka UK.

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

Otsuka Europe noted that as part of its response to a previous case, Case AUTH/3151/1/19 it committed to reviewing all of the prescribing information issued in 2018/19 to ensure that it was consistent with the relevant summaries of product characteristics (SPCs) and otherwise complied with the of the Code.

The Otsuka Europe medical team led a review of current prescribing information earlier in 2019 and concluded that no immediate revisions were required. A review of the prescribing information, focussing on the current SPCs by an independent consultant commenced in early June 2019. This second review showed a number of discrepancies between the SPCs and the prescribing information for four of the five medicines; among other things some potentially serious events were missing and certain warnings had been omitted. Otsuka Europe was still analysing the significance of the errors and omissions; however, given the nature of this voluntary admission, and Otsuka's very recent history with inaccurate prescribing information, it considered it important to notify the PMCPA as soon as it became aware as indicated in its response to Cases AUTH/3041/6/18 and AUTH/3042/6/18, historically its prescribing information had not been of an appropriate standard.

Otsuka Europe submitted that these errors and omissions amounted to a breach of the Code in relation to the content of the prescribing information at issue and associated material. In addition, Otsuka had failed to address adequately issues with a process critical to patient safety, in breach of the Code.

Given the issues above highlighted that procedures were still failing to ensure that there was no inconsistency between SPCs and prescribing information, Otsuka acknowledged that this was a breach of the undertakings provided in Cases AUTH/3041/6/18 and AUTH/3042/6/18 by Otsuka Europe and Otsuka UK respectively. This also amounted to a

breach of the undertaking provided by Otsuka Europe in Case AUTH/3123/11/18. There had also been breaches of Clause 2 by Otsuka UK and Otsuka Europe.

Correspondence from a concerned group of employees was received; this was not treated as a complaint under the Code but Otsuka was provided with anonymised extracts as its response to the points made would be helpful in considering its voluntary admission.

The detailed response from Otsuka is given below.

The Panel noted Otsuka Europe's submission that the second review revealed a number of discrepancies between the SPCs and the prescribing information for four of the five medicines; general examples were referred to and a copy of the results were provided. The Panel noted Otsuka Europe's submission that given its centralised process for prescribing information, similar errors and omissions were likely to be seen in the prescribing information of the European affiliates including Otsuka UK. The Panel noted that there was some internal disagreement regarding the significance of the errors and omissions.

The Panel noted that when it made its voluntary admission, Otsuka was still analysing the significance of the errors and omissions identified by the independent review.

The Panel noted that Otsuka Europe deemed it necessary to withdraw the relevant prescribing information which was available for use on material for between two and eight months depending on the medicine resulting in 33 job bags being withdrawn in Europe and 65 in the UK.

Otsuka had not provided copies of the Jinarc, Abilify, Abilify Maintena and Samsca SPCs so the Panel accessed these on the electronic medicines compendium (eMC) website. The Panel noted that these SPCs had been updated since the voluntary admission had been submitted but upon reviewing the changes outlined on eMC they did not appear to be relevant to the subject of the voluntary admission.

With regard to Jinarc, the Panel noted that the identified errors included the omission of two drug interactions and no date of preparation. The Panel noted that, as acknowledged in the independent review, drug interactions were not specifically required under the Code but, in the Panel's view, it would be helpful if such precautions were included if they were particularly relevant to the indications being advertised. The Panel did not have any of the advertising materials before it but noted that, in any event, drug interactions were included in the Otsuka UK and Otsuka Europe February 2019 Jinarc prescribing information. The Panel noted that the omission of the date the prescribing information was drawn up or last revised as required under the Code was an error identified in the independent review. The Panel noted, however, that both the Otsuka Europe and Otsuka UK Jinarc prescribing information provided, listed the date of preparation as February 2019. The Panel did not consider that the Jinarc prescribing information provided by Otsuka was in breach of the Code based on the omissions identified in the independent review. The Panel had not seen the associated promotional materials which were also the subject of the admission. On the basis that it was implicit that the prescribing information provided, as part of the voluntary admission, was the same as that on the materials at issue the Panel ruled no breach of the Code.

With regard to Abilify and Abilify Maintena which had a shared prescribing information, the Panel noted that the errors identified by the independent review included: the omission of the serious side effect eye pain; the warning/precaution about increased blood pressure; that the word serious had been incorrectly added in front of 'uncommon' and 'not known' frequency; and 'elevated creatinine phosphokinase and rhabdomyolysis have been reported' was omitted from the warnings section; and whilst it stated 'not indicated for treatment of dementia-related psychosis' there was no mention that there was increased mortality in clinical trials in elderly with psychosis associated with Alzheimer's.

The Panel noted from emails provided by Otsuka that the Europe medical team disagreed with the findings and details were provided.

The Panel noted that the prescribing information in question included the subheadings 'Not known (cannot be estimated from the available data) serious side effects' and 'Uncommon serious side effects'. The Panel did not consider that it was necessarily a breach of the Code to use the word 'serious' to designate that those adverse events listed by frequency were serious adverse events that were required to be included in prescribing information under the Code in addition to the common adverse events likely to be encountered.

The Panel noted that both the Otsuka Europe and Otsuka UK May 2019 prescribing information stated in the warnings and precautions section for all formulations 'Not indicated for treatment of dementia-related psychosis'. In the Panel's view, this was sufficient such that the additional statement 'increased mortality in clinical trials in elderly with psychosis associated with Alzheimer's' was not required given that the prescribing information made it clear that such use was in any event not indicated.

The Panel noted that eye pain was listed as an uncommon adverse event in the Abilify Maintena SPC accessed by the Panel on eMC on 18 June for prolonged-release suspension for injection and was not included in the list of adverse events in the prescribing information for that formulation. The Panel did not consider that there was evidence before it to show that eye pain was classified as a serious adverse event that was required to be included in the May 2019 Otsuka UK and Otsuka Europe Abilify and Abilify Maintena prescribing information in relation to the prolonged-release solution for injection formulations.

The Panel noted that the May 2019 Otsuka UK and Otsuka Europe Abilify and Abilify Maintena prescribing information stated within the warnings and precautions section for all formulations that they should be used with caution in patients with conditions predisposing to hypertension. The Panel further noted that increased diastolic blood pressure was listed as an uncommon serious side effect for the 7.5mg/ml solution for injection (IM) and hypertension was listed as a serious side effect of unknown frequency for oral formulations and 7.5mg/ml solution for injection and uncommon for prolonged-release solution for injection in both the May 2019 Otsuka Europe and Otsuka UK prescribing information which was consistent with the respective SPCs.

The Panel noted that increased creatinine phosphokinase was listed as a serious side effect of unknown frequency for oral formulations and the 7.5mg/ml solution for injection and of common frequency for prolonged-release suspension for injection in both the

Otsuka Europe and Otsuka UK May 2019 prescribing information which was consistent with the respective SPCs.

The Panel noted that both neuroleptic malignant syndrome (NMS) and rhabdomyolysis were listed as a serious side effect of unknown frequency for all formulations (oral formulations, 7.5mg/ml solution for injection and prolonged-release suspension for injection) in both the Otsuka Europe and Otsuka UK May 2019 prescribing information which was consistent with the respective SPCs.

The Panel did not consider that there was evidence that the Otsuka Europe and Otsuka UK May 2019 Abilify and Abilify Maintena prescribing information did not contain the information required by the Code. The Panel did not consider that the Abilify and Abilify Maintena May 2019 prescribing information provided by Otsuka was in breach of the Code based on the matters identified in the independent review. The Panel had not seen the associated promotional materials which were also the subject of the admission. On the basis that it was implicit that the prescribing information provided as part of the voluntary admission was the same as that on the materials at issue, the Panel ruled no breach of the Code.

With regard to Samsca, the Panel noted that the errors identified included that: acute hepatic failure had been omitted from the list of unknown serious adverse events; the warnings section listed 'permanent neurological sequelae' when it should provide specific examples of the serious events that could be observed; the warning section stated that Samsca should be interrupted rather than 'interrupted or discontinued'; and it omitted the term 'frequency of' before side effects such that it incorrectly read 'Not known side effects'; and used > rather than ≥ when defining common and very common frequency of side effects. The Panel noted that the updated Samsca prescribing information had not been provided as it had not yet been approved.

In the Panel's view, it was clear that 'not known' in the December 2018 Otsuka UK and October 2018 Otsuka Europe Samsca prescribing information related to the frequency of the adverse events.

The Panel further noted that it was not necessarily a breach of the Code to refer to 'permanent neurological sequelae' rather than list specific examples of such. The Samsca SPC stated 'Too rapid correction of hyponatremia (increase ≥ 12 mmol/L/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma or death' whilst both the Otsuka Europe and Otsuka UK prescribing information stated ' Too rapid hyponatremia correction can cause permanent neurological sequelae, coma or death.

The Panel did not consider that there was evidence that either the use of 'not known' or the reference to 'permanent neurological sequelae' constituted a breach of the Code and thus no breach was ruled in relation to both the Otsuka UK and Otsuka Europe prescribing information.

The Panel noted that acute hepatic failure, listed in the Samsca SPC as frequency not known was included in the Otsuka UK Samsca prescribing information dated December 2018 but not in the Otsuka Europe prescribing information dated October 2018. The Panel had not seen the associated promotional materials which were also the subject of

the admission. On the basis that it was implicit that the prescribing information provided as part of the voluntary admission was the same as that on the materials at issue the Panel ruled no breach of the Code in relation to the Otsuka UK prescribing information dated December 2018 and a breach of the Code in relation to the Otsuka Europe Samsca prescribing information dated October 2018.

The Panel noted that both the Otsuka Europe and Otsuka UK prescribing information stated 'Samsca treatment should be interrupted and hypotonic fluid administered if serum sodium increases ≥12 mmol/L within 24 hours or ≥18 mmol/L within 48 hours' whereas the Samsca SPC accessed by the Panel on the eMC website on 18 June stated 'In case serum sodium increases ≥ 12 mmol/L within 24 hours or ≥ 18 mmol/L within 48 hours, tolvaptan treatment is to be interrupted or discontinued followed by administration of hypotonic fluid'. The Panel further noted that both the Otsuka UK and Otsuka Europe Samsca prescribing information listed very common as >1/10 and common as >1/100 to < 1/10 which was inconsistent with the SPC which described very common as being ≥ 1/10 and common as ≥ 1/100 to < 1/10. The Panel noted that the Otsuka UK prescribing information dated December 2018 and the Otsuka Europe prescribing information dated October 2018 were not consistent with the Samsca SPC in terms of what should occur when serum sodium increased and the definition of frequency of common and very common adverse events. The Panel noted that it had not seen the associated promotional materials which were also the subject of the admission. On the basis that it was implicit that the prescribing information provided as part of the voluntary admission was the same as that on the materials at issue the Panel ruled a breach of the Code in relation to the Otsuka Europe and Otsuka UK prescribing information and associated materials.

The Panel noted its comments and rulings above in relation to the Samsca prescribing information and considered that both Otsuka Europe and Otsuka UK had failed to maintain high standards; a breach of the Code was ruled.

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 information, the omission of which could potentially impact patient safety. A breach of the Code was ruled in relation to both companies.

The Panel noted Otsuka Europe's submission that the issues above highlighted that the process for implementing changes to SPCs was still failing to ensure that there was no inconsistency between SPCs and prescribing information.

The Panel noted that in Case AUTH/3042/6/18 (Otsuka UK) the Panel ruled a breach of the Code in relation to Jinarc prescribing information which omitted a contraindication and was, therefore, inconsistent with the SPC current at that time, and was not up-to-date and a breach of the Code in relation to five Abilify Maintena materials that Otsuka submitted did not contain the latest version of prescribing information.

The Panel noted that in Case AUTH/3041/6/18 (Otsuka Europe) the Panel ruled breaches of the Code in relation to 7 Jinarc promotional materials issued by Otsuka Europe related to a website that did not contain the latest version of the prescribing information.

In Case AUTH/3123/11/18 Otsuka Europe was ruled in breach of the Code as it had failed to timely and robustly address inadequacies in a critical process (updating prescribing information) that had the potential to impact patient safety.

The Panel noted that in this case in relation to the Samsca prescribing information Otsuka Europe had failed to comply with its undertakings in Cases AUTH/3041/6/18 and AUTH/3123/11/18 and Otsuka UK its undertaking in Case AUTH/3042/6/18. The Panel therefore ruled a breach of the Code in relation to Otsuka UK and two breaches of the Code in relation to Otsuka Europe.

The Panel considered that in failing to identify the issues with the prescribing information prior to the independent review and having prescribing information which was inconsistent with the SPC current at that time, and was not up-to-date on materials available for Samsca for up to eight months meant that both Otsuka Europe and Otsuka UK had failed to maintain high standards and a breach of the Code was ruled.

The Panel noted the importance of undertakings and considered that failure to comply with the undertakings and assurance previously given meant that Otsuka Europe and Otsuka UK had brought discredit upon, and reduced confidence in, the pharmaceutical industry. The Panel thus ruled a breach of the Code.

Otsuka Pharmaceuticals Europe Ltd and Otsuka Pharmaceuticals UK Ltd admitted breaches of the Code in that there were errors and omissions in the current prescribing information for four of its medicines:

- Abilify (aripiprazole)
- Abilify Maintena (aripiprazole)
- Jinarc (tolvaptan)
- Samsca (tolvaptan)

Otsuka Europe stated that given its centralised process for the drafting and revision of prescribing information for all of its medicines that had authorisations in Europe, similar errors and omissions were likely to be seen in the prescribing information of the affiliates, and had been seen in the current prescribing information used by Otsuka UK. It was for this reason that the voluntary admission was made jointly between Otsuka Europe and Otsuka UK.

Otsuka Europe stated that it had initiated a European wide recall of the impacted prescribing information and any associated material. This would be completed by 26 June 2019.

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

VOLUNTARY ADMISSION

Otsuka Europe noted that as part of its response to Case AUTH/3151/1/19 it committed to reviewing all of the prescribing information issued in 2018/19 for its currently marketed medicines to ensure that they were consistent with the relevant summaries of product characteristics (SPCs) and in all other ways complied with the requirements of Clause 4.2. The currently marketed medicines at issue were Abilify, Abilify Maintena, Jinarc and Samsca .

A review of current prescribing information earlier in 2019, led by the Otsuka Europe medical team, concluded that no immediate revisions were required. A further evaluation of the prescribing information by an independent external medical affairs consultant commenced in early June 2019. Given that the content of prescribing information had the potential to impact on patient safety, the external consultant focused on the current SPCs and prescribing information.

On 20 June 2019, senior management from Otsuka Europe and Otsuka UK discussed the results of the second, independent, review and it was clear that there were a number of discrepancies between the SPCs and the prescribing information for four medicines. For example, some potentially serious events were missing, certain warnings had been omitted and the word 'unknown' had been used to describe adverse events in some prescribing information without making it clear that this related to the frequency of the event, rather than whether the event itself had been observed in post-marketing studies.

The results of the second review of the current prescribing information were provided. Otsuka Europe was still analysing the significance of the errors and omissions; however, given the nature of this voluntary admission, and Otsuka's very recent history with inaccurate prescribing information, it considered it important to notify the PMCPA as soon as it became aware as indicated in its response to Cases AUTH/3041/6/18 and AUTH/3042/6/18, historically its prescribing information had not been of an appropriate standard.

Otsuka Europe submitted that these errors and omissions amounted to a breach of Clauses 4.1 and 4.2 in relation to the content of the prescribing information at issue and associated material. Further, given that Otsuka had failed to adequately address issues with a process critical to patient safety, this amounted to a breach of Clause 9.1.

The issues above highlighted that the process for implementing changes to SPCs was still failing to ensure that there was no inconsistency between SPCs and prescribing information, Otsuka acknowledged that this was a breach of the undertakings provided in Cases AUTH/3041/6/18 and AUTH/3042/6/18 by Otsuka Europe and Otsuka UK respectively. This also amounted to a breach of the undertaking provided by Otsuka Europe in Case AUTH/3123/11/18. Thus, there had been a breach of Clause 29 by Otsuka UK and two breaches of Clause 29 by Otsuka Europe. There had also been a breach of Clause 2 by Otsuka UK and two breaches of Clause 2 by Otsuka Europe. This was of course completely unacceptable and Otsuka sincerely apologised.

Otsuka was asked to provide the Authority with any further comments in relation to the requirements of Clauses 2, 4.1, 4.2, 9.1 and 29 of the Code.

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Correspondence from a concerned group of employees was received; this was not treated as a complaint under the Code but anonymised extracts were provided to Otsuka as its response to the points made would be helpful in considering its voluntary admission.

The anonymised extracts referred to the following:

1 Alleged lack of action in dealing with commitments to the PMCPA

The employees stated that staff were recently briefed that some of the obligations to the PMCPA had not been met during an offsite meeting led by Otsuka UK.

Some of the more concerning areas included:

- Inaccurate prescribing information
  There were fears that even the current prescribing information was incorrect, which was not true, especially as these had already been checked by medical and regulatory affairs at a European level. It seemed that it was a futile exercise or perhaps another attempt to blame the medical team in Otsuka Europe. It was suggested that the PMCPA sought confirmation from Otsuka that all prescribing information was accurate, bearing in mind the patient safety element.

- Alleged lack of trust in signatories
  Staff were informed by senior management that the medical signatories were not able to certify material until retraining had occurred. This decision was not made in consensus or shared earlier (given that the commitment was given to the PMCPA at least 3 months earlier) and seemed to be blaming the medical team for what had been an organization failure (the lack of proper process), the blame culture at Otsuka continued. Moreover, an external signatory has been brought in to certify material and employees queried what made him/her more qualified than the current signatories.

  The medical team had also been forced to undergo external revalidation organized by an external compliance agency – the very same third party that the group of employees had concerns about (conflict of interest and competence).

The employees queried if the organization would take responsibility for lack of governance.

2 Prescribing information.

The group of employees provided an update stating that there was a meeting on Thursday, 20 June at Otsuka UK when it was decided that Abilify Maintena, Jinarc and Samsca did not have all the necessary safety information, and a withdrawal was initiated by Otsuka UK.

No Otsuka Europe medical team member was invited to the meeting. The group of employees queried how a decision could be made when the true product experts were not present. Furthermore, reference was made to receiving confirmation from an employee in pharmacovigilance(PV) that there were no patient safety information missing from the prescribing information.

This was said to prove that there was an ulterior motive by Otsuka UK, the external consultant who carried out the assessment and certain members of the European pharmaceutical leadership team to discredit Otsuka Europe medical team members.

This should be investigated by the PMCPA urgently, especially when individuals in the organization did not seem to take patient safety seriously.

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RESPONSE
Neither Otsuka Europe nor Otsuka UK had any further comment on the relevant clauses. The companies provided details of the 98 job bags which had had to be withdrawn by either Otsuka Europe or Otsuka UK and the dates during which the prescribing information at issue had been available for use on material (variously from between 5 November 2018 and 26 June 2019).

Otsuka's response to correspondence from a concerned group of employees

1 Alleged lack of action in dealing with commitments to the PMCPA

The offsite meeting referred to was organised and co-led by Otsuka Europe and Otsuka UK under the CORE programme, not Otsuka UK alone. The agenda was provided.

Otsuka stated that the meeting objective was to ensure all those potentially involved in the PMCPA audit had up-to-date information regarding the complaints received and ongoing remediation activities. In addition, a presentation was given on what to expect on the days of the audits and staff were given an opportunity to have a mock interview (informal or formal). Otsuka stated that it had been tracking all of its obligations (referring to them as commitments) to the PMCPA as part of the CORE Programme.

Otsuka stated that a number of the commitments had been delayed due to a lack of leadership in certain areas. As the company worked to rectify these internal leadership challenges, it was important for all staff to be aware of on-going remediation activities and, where relevant, timelines for completion were amended. A tracker of the commitments and related progress was provided.

<u>Inaccurate prescribing information</u>

Otsuka noted, as detailed in the voluntary admissions, given the issues that Otsuka Europe and Otsuka UK had had in relation to the accuracy and completeness of prescribing information, a commitment was made to the PMCPA that a comprehensive review would be conducted of the current prescribing information for all Otsuka medicines promoted in the UK.

As the concerned group of employees noted, this was initially conducted by a team led by the Otsuka Europe medical department. However, given that this review was by those that drafted and/or certified the documents that were being checked, and given the importance for the prescribing information to reflect the applicable SPC, Otsuka Europe considered it important that this review was also conducted by an external consultant.

This was not a futile exercise and indeed, Otsuka Europe discovered some potentially significant issues with three of the four prescribing information documents that were reviewed, resulting in the withdrawal of the relevant prescribing information and associated material, and this voluntary admission.

<u>Alleged lack of trust in signatories</u>

Otsuka stated that the group of employees were correct in that Otsuka Europe had decided to temporarily remove signatory status from members of its medical team. This was a very difficult decision to take, but was necessary, given the number of compliance issues recently identified with material eg, inaccurate and incomplete prescribing information, material relevant to

previous cases such as Case AUTH/3153/1/19 and a recent job bag audit (report provided) which identified multiple critical findings.

Signatories had a critical role, being the final gatekeeper for materials and activities for any pharmaceutical company that had committed to comply with the Code. In the past, Otsuka Europe had failed to appropriately train and validate its signatories, a fact that had no doubt contributed to the situation that it now faced. It was thus vitally important to support the signatories and, until such time as training and validation was complete, to remove them from the list of signatories for the purposes of certification and examination of material and activities. This decision was communicated to a senior medical employee in late May 2019.

In relation to validation, Otsuka stated that the group of employees were incorrect that they were being forced to take one particular validation. As with the training, the nature and format of the validation was discussed and agreed with a senior medical employee. It had yet to take place but was being developed and conducted by a supplier other than the one referred to who was selected by the Otsuka Europe medical team.

In the meantime, Otsuka Europe was using the services of a medical affairs consultant (details of whom were notified to the PMCPA and MHRA on 5 June 2019) who had extensive experience in relation to certification of material and achieved 97.5% in the validation completed for the purposes of being a signatory at Otsuka Europe.

Otsuka Europe absolutely took responsibility for the lack of governance in relation to material and activities and submitted it was addressing this as a matter of urgency. It appreciated that the decisions led to discord within certain functions in the company, but it would be irresponsible to permit signatories to remain so without providing training that had been lacking in the past on the practical application of the Code. Other measures were also being taken, for example the development of detailed procedures for Otsuka Europe, which should provide further guidance on the review and approval of materials and activities.

2 Prescribing information update

Otsuka noted that the group of employees referred to the meeting which gave rise to the voluntary admission and took place on 20 June to discuss the results of the review of prescribing information conducted by the medical affairs consultant.

Given that the meeting objective was to discuss errors and omissions in prescribing information and that members of the medical team authored and/or certified the prescribing information at issue, it was anticipated that having this team present might lead to significant conflict and disagreement with the results of the review. It was important that an objective view was maintained, permitting a constructive discussion and assessment of next steps.

Once the decision was made to withdraw certain prescribing information and associated material, this and the agreed next steps (as well as the results of the review) were communicated to a senior medical employee at Otsuka Europe.

Otsuka Europe submitted that the comment that there were no ‘true product experts’ at the meeting was not true; many of those in the room were from both medical and commercial functions and had worked on the relevant medicines for a number of years. Otsuka Europe

also noted that the discussion at the meeting was in relation to the prescribing information vs the SPC and the requirements of the Code.

There was no intent in any of these activities to discredit the Otsuka Europe medical team. The objective of the review and the discussion was to verify that the prescribing information for all of the Otsuka medicines promoted in Europe was complete, accurate and complied with the Code.

With regard to confirmation from PV that there was 'no patient safety information missing' from the prescribing information, there was an internal communication in relation to the Abilify and Abilify Maintena prescribing information wherein it was indeed stated by an employee in PV that '…we believe that the relevant required information from the [SPC] has been reflected in the [prescribing information] and therefore no information that could potentially compromise patients' safety has been omitted'.

However, as communicated in the initial voluntary admission in these cases, the review revealed that some potentially serious adverse events were missing, certain warnings had been omitted and the word 'unknown' had been used to describe adverse events in some prescribing information without making it clear that this related to the frequency of the event, rather than whether the event itself has been observed in post-marketing reports.

Clearly there was some internal disagreement regarding the significance of these errors and omissions. However, given that there was a discrepancy between the SPC and the prescribing information, which could potentially impact patient safety, Otsuka Europe deemed it necessary to withdraw the relevant prescribing information. It was reviewing the working practice document in relation to the development and update of prescribing information to ensure that all relevant stakeholders were involved.

Given all of the additional comments from the group of employees, it was quite obvious that a number of employees within Otsuka Europe were very unhappy and disappointed with the organisation and Otsuka Europe recognised that a lack of effective leadership, poor processes and an absence of focus on compliance over a number of years had significantly contributed to this culture. Otsuka committed as an organisation, and with input from the PMCPA, to work as a team to address and rectify these issues.

PANEL RULING

The Panel noted that Jinarc, Abilify, Abilify Maintena and Samsca were the subject of this voluntary admission. 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.

The Panel noted that the case preparation manager had provided Otsuka with comments made to the PMCPA by individuals who described themselves as 'a group of concerned employees'. The Panel noted that insofar as these comments raised new matters such matters would not be considered as part of the voluntary admission.

The Panel noted that following a review of Otsuka's current prescribing information by the Otsuka Europe medical team in early 2019, a second review was conducted by an independent consultant in June 2019. The Panel noted Otsuka Europe's submission that the second review

revealed a number of discrepancies between the SPCs and the prescribing information for the four medicines in question; general examples were referred to and a copy of the results were provided. The Panel noted Otsuka Europe's submission that given the centralised process that it followed for the drafting and revision of prescribing information for all its medicines that had authorisations in Europe, similar errors and omissions were likely to be seen in the prescribing information of the affiliates including Otsuka UK. The Panel noted that there was some internal disagreement regarding the significance of the errors and omissions.

The Panel noted that when it submitted its voluntary admission, Otsuka was still analysing the significance of the errors and omissions identified by the independent review but considered it was important to notify the PMCPA as soon as it became aware of the issue due to the company's history with inaccurate prescribing information.

The Panel noted that Otsuka Europe deemed it necessary to withdraw the relevant prescribing information which was available for use on material for between two and eight months depending on the medicine resulting in 33 job bags being withdrawn in Europe and 65 in the UK.

The Panel noted 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, among other things, contraindications 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 Clause 4.2 listed the components of prescribing information which had to be provided including, *among other* things, 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 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 prescribing information.

The Panel noted that Otsuka had not provided copies of the Jinarc, Abilify, Abilify Maintena and Samsca SPCs so the Panel accessed these on the electronic medicines compendium (eMC) website when considering the case. The Panel noted that these SPCs had been updated since the voluntary admission had been submitted but upon reviewing the changes outlined on the eMC they did not appear to be relevant to the subject of the voluntary admissions.

The Panel noted that according to Otsuka Europe and Otsuka UK, the job bags referred to above contained incorrect prescribing information which was inconsistent with the SPC current at that time, was not up-to-date and was therefore in breach of Clause 4.1.

With regard to Jinarc, the Panel noted that the identified errors included the omission of two drug interactions and no date of preparation. The omitted drug interactions included that potent CYP3A inducers decreased Jinarc exposure and efficacy and therefore concomitant use was to be avoided and that the effect of vasopressin analogues to prevent or control bleeding might be attenuated when co-administered with Jinarc and therefore co-administration was not recommended. The Panel noted that, as acknowledged in the independent review, drug interactions were not specifically required under Clause 4.2 but, in the Panel's view, it would be helpful if such precautions were included if they were particularly relevant to the indications being advertised. The Panel did not have any of the advertising materials before it but noted that, in any event, drug interactions were included in the Otsuka UK and Otsuka Europe February 2019 Jinarc prescribing information. Both stated that caution should be exercised with

CYP3A inducers and that the effect of vasopressin analogues, eg desmopressin used to prevent or control bleeding, might be attenuated. The Panel noted that the omission of the date when the prescribing information was drawn up or last revised as required under Clause 4.2 was an error identified in the independent review. The Panel noted, however, that both the Otsuka Europe and Otsuka UK Jinarc prescribing information provided listed the date of preparation as February 2019. The Panel noted that, when the voluntary admission was submitted, Otsuka was still analysing the significance of the errors and omissions identified by the independent review. The Panel did not consider that the Jinarc prescribing information provided by Otsuka was in breach of Clause 4.1 based on the omissions identified in the independent review. The Panel noted that it had not seen the associated promotional materials which were also the subject of the admission. On the basis that it was implicit that the prescribing information provided, as part of the voluntary admission, was the same as that on the materials at issue, the Panel ruled no breach of Clause 4.1.

With regard to Abilify and Abilify Maintena which had a shared prescribing information, the Panel noted that the errors identified by the independent review included: the omission of the serious side effect eye pain; the warning/precaution about increased blood pressure; that the word serious had been incorrectly added in front of 'uncommon' and 'not known' frequency; and 'elevated creatinine phosphokinase and rhabdomyolysis have been reported' was omitted from the warnings section; and whilst it stated 'not indicated for treatment of dementia-related psychosis' there was no mention that there was increased mortality in clinical trials in the elderly with psychosis associated with Alzheimer's. The Panel noted that when the voluntary admission was submitted Otsuka was still analysing the significance of the errors and omissions identified by the independent review.

The Panel noted from emails provided by Otsuka that the Otsuka Europe medical team disagreed with the findings and stated that 'serious' had been correctly added next to unknown and uncommon frequency because for those frequencies they were the only adverse events that were required to be included in the prescribing information. The medical team was further of the view that phosphokinase and rhabdomyolysis were part of neuroleptic malignant syndrome (NMS) which it considered every clinician was trained to know and both of which were included as a warning in the May 2019 prescribing information. The Otsuka Europe medical team further noted that Alzheimer's was a form of dementia which was covered and that in its view eye pain was not a serious adverse event and neither was increased blood pressure but there were specific hypertensive conditions that were.

The Panel noted that the prescribing information in question included the subheadings 'Not known (cannot be estimated from the available data) serious side effects' and 'Uncommon serious side effects'. The Panel did not consider that it was necessarily a breach of the Code to use the word 'serious' 'to designate that those adverse events listed by frequency were serious adverse events that were required to be included in prescribing information under Clause 4.2 in addition to the common adverse events likely to be encountered.

The Panel noted that both the Otsuka Europe and Otsuka UK May 2019 prescribing information stated in the warnings and precautions section for all formulations 'Not indicated for treatment of dementia-related psychosis'. In the Panel's view, the clear statement that it was not indicated for dementia-related psychosis was sufficient such that the additional statement 'increased mortality in clinical trials in elderly with psychosis associated with Alzheimer's' was not required given that the prescribing information made it clear that such use was in any event not indicated.

The Panel noted that eye pain was listed as an uncommon adverse event in the Abilify Maintena SPC accessed by the Panel on eMC on 18 June for prolonged-release suspension for injection and was not included in the list of adverse events in the prescribing information for this formulation. The Panel did not consider that there was evidence before it to show that eye pain was classified as a serious adverse event that was required to be included in the May 2019 Otsuka UK and Otsuka Europe Abilify and Abilify Maintena prescribing information in relation to the prolonged-release solution for injection formulations.

The Panel noted that the May 2019 Otsuka UK and Otsuka Europe Abilify and Abilify Maintena prescribing information stated within the warnings and precautions section for all formulations that they should be used with caution in patients with conditions predisposing to hypertension. The Panel further noted that increased diastolic blood pressure was listed as an uncommon serious side effect for the 7.5mg/ml solution for injection (IM) and hypertension was listed as a serious side effect of unknown frequency for oral formulations and 7.5mg/ml solution for injection and uncommon for prolonged-release solution for injection in both the May 2019 Otsuka Europe and Otsuka UK prescribing information which was consistent with the respective SPCs.

The Panel noted that increased creatinine phosphokinase was listed as a serious side effect of unknown frequency for oral formulations and the 7.5mg/ml solution for injection and of common frequency for prolonged-release suspension for injection in both the Otsuka Europe and Otsuka UK May 2019 prescribing information which was consistent with the respective SPCs.

The Panel noted that both neuroleptic malignant syndrome (NMS) and rhabdomyolysis were listed as a serious side effect of unknown frequency for all formulations (oral formulations, 7.5mg/ml solution for injection and prolonged-release suspension for injection) in both the Otsuka Europe and Otsuka UK May 2019 prescribing information which was consistent with the respective SPCs.

The Panel noted that when the voluntary admission was submitted, Otsuka was still analysing the significance of the errors and omissions identified by the independent review. The Panel did not consider that there was evidence that the Otsuka Europe and Otsuka UK May 2019 Abilify and Abilify Maintena prescribing information did not contain the information required by Clause 4.2. The Panel did not consider that the Abilify and Abilify Maintena May 2019 prescribing information provided by Otsuka was in breach of Clause 4.1 based on the matters identified in the independent review. The Panel noted that it had not seen the associated promotional materials which were also the subject of the admission. On the basis that it was implicit that the prescribing information provided as part of the voluntary admission was the same as that on the materials at issue the Panel ruled no breach of Clause 4.1

With regard to Samsca, the Panel noted that the errors identified included that: acute hepatic failure had been omitted from the list of unknown serious adverse events; the warnings section listed ‘permanent neurological sequelae’ when it should have provided specific examples of the serious events that could be observed; the warning section stated that Samsca should be interrupted rather than ‘interrupted or discontinued’; and it omitted the term ‘frequency of’ before side effects such that it incorrectly read ‘Not known side effects’; and used > rather than ≥ when defining common and very common frequency of side effects. The Panel noted that the updated Samsca prescribing information had not been provided as it had not yet been approved.

In the Panel's view, it was clear that 'not known' in the December 2018 Otsuka UK and October 2018 Otsuka Europe Samsca prescribing information related to the frequency of the adverse events.

The Panel further noted that it was not necessarily a breach of the Code to refer to 'permanent neurological sequelae' rather than list specific examples of such. The Samsca SPC stated 'Too rapid correction of hyponatremia (increase ≥ 12 mmol/L/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma or death' whilst both the Otsuka Europe and Otsuka UK prescribing information stated 'Too rapid hyponatremia correction can cause permanent neurological sequelae, coma or death'.

The Panel did not consider that there was evidence that either the use of 'not known' or the reference to 'permanent neurological sequelae' constituted a breach of Clause 4.1 and thus no breach was ruled in relation to both the Otsuka UK and Otsuka Europe prescribing information.

The Panel noted that acute hepatic failure, listed in the Samsca SPC as frequency 'not known' was included in the Otsuka UK Samsca prescribing information dated December 2018 but not in the Otsuka Europe prescribing information dated October 2018. The Panel noted that it had not seen the associated promotional materials which were also the subject of the admission. On the basis that it was implicit that the prescribing information provided as part of the voluntary admission was the same as that on the materials at issue, the Panel ruled no breach of Clause 4.1 in relation to the Otsuka UK prescribing information dated December 2018 and a breach of Clause 4.1 in relation to the Otsuka Europe Samsca prescribing information dated October 2018.

The Panel noted that both the Otsuka Europe and Otsuka UK prescribing information stated 'Samsca treatment should be interrupted and hypotonic fluid administered if serum sodium increases ≥12 mmol/L within 24 hours or ≥18 mmol/L within 48 hours whereas the Samsca SPC accessed on the eMC website on 18 June stated 'In case serum sodium increases ≥12 mmol/L within 24 hours or ≥18 mmol/L within 48 hours, tolvaptan treatment is to be interrupted or discontinued followed by administration of hypotonic fluid'. The Panel further noted that both the Otsuka UK and Otsuka Europe Samsca prescribing information listed very common as >1/10 and common as >1/100 to < 1/10 which was inconsistent with the SPC which described very common as being ≥1/10 and common as ≥1/100 to < 1/10. The Panel noted that the Otsuka UK prescribing information dated December 2018 and the Otsuka Europe prescribing information dated October 2018 were not consistent with the Samsca SPC in terms of what should occur when serum sodium increased and the definition of frequency of common and very common adverse events. The Panel noted that it had not seen the associated promotional materials which were also the subject of the admission. On the basis that it was implicit that the prescribing information provided as part of the voluntary admission was the same as that on the materials at issue, the Panel ruled a breach of Clause 4.1 in relation to the Otsuka Europe and Otsuka UK prescribing information and associated materials.

The Panel noted its comments and rulings above in relation to the Samsca prescribing information and considered that both Otsuka Europe and Otsuka UK had failed to maintain high standards; a breach of Clause 9.1 was ruled.

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 information, the omission of which could potentially impact patient safety. A breach of Clause 2 was ruled in relation to both companies.

The Panel noted Otsuka Europe's submission that the issues above highlighted that the process for implementing changes to SPCs was still failing to ensure that there was no inconsistency between SPCs and prescribing information.

The Panel noted that in Case AUTH/3042/6/18 (Otsuka UK) the Panel ruled a breach of Clause 4.1 in relation to Jinarc prescribing information which omitted a contraindication and was, therefore, inconsistent with the SPC current at that time, and was not up-to-date and a breach of Clause 4.1 in relation to five Abilify Maintena materials that Otsuka submitted did not contain the latest version of prescribing information.

The Panel noted that in Case AUTH/3041/6/18 (Otsuka Europe) the Panel ruled breaches of Clause 4.1 in relation to 7 Jinarc promotional materials issued by Otsuka Europe related to a website that did not contain the latest version of the prescribing information.
In Case AUTH/3123/11/18 Otsuka Europe was ruled in breach of the Code as it had failed to timely and robustly address inadequacies in a critical process (updating prescribing information) that had the potential to impact patient safety.

The Panel noted that in this case, in relation to the Samsca prescribing information, Otsuka Europe had failed to comply with its undertakings in Cases AUTH/3041/6/18 and AUTH/3123/11/18 and Otsuka UK its undertaking in Case AUTH/3042/6/18. The Panel therefore ruled a breach of Clause 29 in relation to Otsuka UK and two breaches of Clause 29 in relation to Otsuka Europe.

The Panel considered that in failing to identify the issues with the prescribing information before the independent review and having prescribing information which was inconsistent with the SPC current at that time, and was not up-to-date on materials available for Samsca for up to eight months, meant that both Otsuka Europe and Otsuka UK had failed to maintain high standards; a breach of Clause 9.1 was ruled.

The Panel noted the importance of undertakings and considered that failure to comply with the undertakings and assurance previously given meant that Otsuka Europe and Otsuka UK had brought discredit upon, and reduced confidence in, the pharmaceutical industry. The Panel thus ruled a breach of Clause 2.

Complaint received **25 June 2019**

Case completed **3 July 2020**