CASE AUTH/3212/6/19 and AUTH/3262/6/19

HEALTH PROFESSIONAL v OTSUKA UK AND OTSUKA EUROPE

Alleged pre licence promotion

An anonymous health professional complained that an online press release about ASTX727, a fixed dose combination of cedazuridine and decitabine being studied for the possible treatment of myelodysplastic syndrome (MDS) and chronic myelomonocytic leukaemia (CML), promoted an unlicensed medicine and contained many inaccuracies and claims that could not be substantiated. ASTX727 was being studied for the possible treatment of myelodysplastic syndromes (MDS) and chronic myelomonocytic leukaemia (CMML). The press release had been jointly released by Astex Pharmaceuticals Inc in the US, a wholly owned subsidiary of Otsuka Pharmaceuticals Co Ltd, and Otsuka Pharmaceutical Co Ltd in Japan (OPCJ).

The matter was taken up with Otsuka (UK) Limited and Otsuka Pharmaceuticals Europe Limited as the UK based affiliates were responsible for the acts/omissions of overseas affiliates that came within the scope of the Code.

The press release detailed the results of the phase III ASCERTAIN Study and the complainant noted that it stated that safety and clinical activity were similar to that observed in a previous phase I/II study; there was, however, no indication as to what those results were and if they were in keeping with what would be expected from such treatments.

The complainant alleged that claims about 'alleviating the significant burden of IV infusions' and survival benefit of 'several months or years' were promotional, encouraged patients to ask their doctors for this medicine and gave them false hope that they might survive many years if they took this medicine. The complainant further noted that clams about the gastrointestinal side effects of ASTX727 were inconsistent with the decitabine summary of products characteristics (SPC).

Amongst other things, the complainant queried the relevance of the press release for a UK audience given that it was focussed on North America and did not mention the UK or Europe. Decitabine was not even approved for MDS/CMML in Europe or the UK but the press release misleadingly implied that it could be used for those indications in Europe. The complainant was also concerned that the press release promoted oral therapy especially with the context of 'alleviating the significant burden of IV infusions' and that by mentioning other studies which were nothing to do with the ASCERTAIN Study, the press release promoted the use of ASTX727 in untested areas with potential dangers for patient safety. The complainant also considered that a reference to Astex expanding the evaluation of cedazuridine/decitabine combinations through a program of investigator-sponsored trials would encourage physicians to contact the company to enquire about or submit proposals for investigator-sponsored studies.

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

The first matter for the Panel to consider was whether the press release was covered by the Code. The Panel noted that although the press release was issued by Astex in the US and Otsuka Japan, and that Otsuka Europe and Otsuka UK did not issue, approve for issue or authorize the material and there was no mention of use of the medicine in the UK or Europe ,it was, however a clearly established principle under the Code that the UK company was responsible for acts and omissions of its overseas affiliates that came within the scope of the Code.

The Panel noted that it appeared that the complainant had accessed the press release via a UK website. The Panel noted that the press release was circulated via a third party by Astex Pharmaceuticals Inc which was a wholly owned subsidiary of Otsuka Pharmaceuticals Co Ltd. A list of the third party's circuits for press releases was provided by Otsuka which included circuits for the UK and Ireland. The Panel noted from emails provided by Otsuka Europe and Otsuka UK that both knew that the press release would be issued in the UK and Ireland.

The Panel noted the companies' submission that Astex approached Otsuka Europe's communications team which liaised with Otsuka UK and a review of the press release using Zinc was initiated. The Panel queried why that review was not completed given that emails stated that 'we have to put joint Astex/Otsuka press releases through [Otsuka UK] review if released in the UK'.

The Panel considered that given the circulation to UK outlets via the third party, the press release was covered by the UK Code. The Panel noted the involvement of Otsuka Europe and Otsuka UK.

The Panel noted that the press release referred to the safety and clinical activity of ASTX727 being similar to that observed in a previous study. It was stated in the press release that the outcome demonstrated that the fixed dose combination enabled '…successful oral delivery of decitabine alleviating the significant burden of five days of monthly IV infusions for patients who might continue to benefit from the drug for several months or even years'. It was further stated that ASTX727 could bring a new treatment option to patients with 'these deadly diseases'. The press release also stated that 'ASTX727 is an investigational compound and is not currently approved in any country'.

The Panel noted Otsuka's submission that although decitabine was licensed in the UK, the combination with cedazuridine (ASTX727) was not and that in the UK decitabine IV was licensed for newly diagnosed, *de novo*, or secondary acute myeloid leukaemia. The Panel also noted that the ASCERTAIN Study was a pharmacokinetic equivalence study and that safety and efficacy were secondary endpoints. The Panel agreed with Otsuka that statements about alleviating the burden of IV infusions, survival benefit, low level of gastrointestinal adverse events and the benefit of oral treatment were thus misleading and not capable of substantiation. The Panel ruled breaches of the Code as acknowledged by Otsuka UK and Otsuka Europe. There did not appear to be clinical evidence to support the claims for ASTX727 and gastrointestinal side effects and a further breach of the Code was ruled.

The Panel noted that ASTX727 was not classified as a prescription only medicine. Relevant clauses of the Code regarding relations with the public only applied to

prescription only medicines. On this very narrow technical point the Panel ruled no breach of those clauses of the Code. However, the Panel considered that the press release issued to the public promoted an unlicensed medicine which meant high standards had not been maintained. A breach of the Code was ruled.

The Panel queried whether the press release should have been distributed in the UK given that ASTX727 was not licensed and the indications for the IV formulation of one of its components was different in the UK compared with the US. The Panel noted Otsuka's submission that the inclusion of such US focused data did not necessarily mean that the press release would not be of interest to a non-US audience. On balance the Panel ruled no breach of the Code based on the narrow allegation.

Given the circumstances the Panel did not consider that the distribution of the press release for an unlicensed medicine in itself meant that that medicine had been promoted. Nor did the Panel consider that the mention of other studies in the clinical programme necessarily promoted the medicine for those indications. It was not unreasonable to give an overview. The Panel noted its rulings above about the content of the press release and in addition considered that some of the language within it was promotional as acknowledged by Otsuka Europe and Otsuka UK. The Panel therefore ruled a breach of the Code in relation to ASTX727. Decitabine IV was licensed in the UK albeit for a different indication than that referred to in the press release and therefore the Panel ruled a breach of the Code.

The Panel considered that high standards had not been maintained with regard to the information about the study outcomes as ruled in breach of the Code above. The Panel therefore ruled a further breach of the Code.

The Panel noted that a breach of Clause 2 was used as a sign of particular censure and was reserved for such use. The Panel considered that the circumstances did not amount to a breach of Clause 2 and ruled accordingly.

An anonymous health professional complained about an online press release about ASTX727, a fixed dose combination of cedazuridine and decitabine which was being studied for the possible treatment of myelodysplastic syndromes (MDS) and chronic myelomonocytic leukaemia (CMML). The press release had been jointly released by Astex Pharmaceuticals Inc in the US, a wholly owned subsidiary of Otsuka Pharmaceuticals Co Ltd, and Otsuka Pharmaceutical Co Ltd in Japan (OPCJ).

The matter was taken up with Otsuka (UK) Limited and Otsuka Pharmaceuticals Europe Limited as the UK based affiliates were responsible for the acts/omissions of overseas affiliates that came within the scope of the Code.

The press release detailed the results of the phase III ASCERTAIN Study.

COMPLAINT

The complainant alleged that the press release was promotional and contained many inaccuracies and claims that could not be substantiated.

The complainant noted that the press release stated that the safety and clinical activity of ASTX727 were similar to that observed in a previous phase I/II study but there was no indication as to what those results were and if they were in keeping with what would be expected from such treatments.

The complainant alleged that claims about 'alleviating the significant burden of IV infusions' and survival benefit of 'several months or years' were promotional; they encouraged patients to ask their doctors for this medicine and gave them false hope that they might survive many years if they took this medicine.

The complainant noted that the study was in MDS and CMML and that various US epidemiological data about these conditions were given but there was no mention of any UK epidemiology. The press release was available in the UK via UK-based media, but it seemed entirely focussed on North America; it only mentioned US and Canadian sites and did not mention the UK or Europe. In fact, decitabine was not even approved for MDS/CMML in Europe or the UK so the press release gave a misleading impression that the medicine could be used for those indications in Europe. It was also not made clear upfront that this was an investigational compound and had not been approved in the UK. This information was included further down the body of the press release but was easily overlooked and the prior information gave a misleading impression.

There were claims about the safety of the medicine in the press release and a statement that it was similar to that of IV decitabine, but of particular note, had a low level of gastrointestinal side effects. This claim promoted a better safety profile as the decitabine summary of products characteristics (SPC) cited vomiting and diarrhoea as occurring very commonly.

The complainant noted that the press release mentioned other studies in the clinical programme (eg low dose formulation, all-oral combinations) which were nothing to do with the ASCERTAIN study which was the primary topic of the press release and thus it promoted the use of the medicine in these untested areas with potential dangers for patient safety.

The press release also stated that 'Astex is also expanding the evaluation of cedazuridine – decitabine combinations through a program of investigator-sponsored trials' which again had nothing to do with the news of the ASCERTAIN study and clearly encouraged physicians to contact the company to enquire about, or submit proposals for, investigator-sponsored studies.

The press release stated, 'The hypomethylating agents decitabine and azacitidine are effective treatment modalities for hematologic cancers and are FDA-approved for the treatment of higher risk MDS and CMML. These agents are administered by IV infusion, or by large volume subcutaneous injections.' There was no reference to the indications in the UK which gave a misleading impression that the indications were the same in the UK. It also disparaged these medicines regarding the mode of administration, did not clearly indicate the volume involved in subcutaneous injections and by stating they were 'large' might discourage patients from accepting these treatments. Thus the press release promoted oral administration, especially with the context of 'alleviating the significant burden of IV infusions' and thus promoted ASTX727.

Overall the complainant questioned the relevance of the press release for a UK audience given that the study was conducted in North America only, a new drug application (NDA) would be submitted to the FDA with no mention of trial or submission in Europe or the UK and the

indication for decitabine was not the same in the UK as it was in the US. It appeared that the press release was being used to promote the medicine prior to it having a licence and to encourage UK physicians to submit investigator-sponsored study proposals.

The complainant understood that press releases were checked to ensure they did not contravene the Code and so he/she queried the competence of those who checked the press release at issue as well the intentions of those who wrote it.

When writing to Otsuka UK and Otsuka Europe, the Authority asked it to consider the requirements of Clauses 2, 3.1, 3.2, 7.2, 7.4, 7.9, 9.1, 11.1, 26.1 and 26.2 of the Code.

RESPONSE

In its initial response Otsuka Europe submitted that the press release was not released with the authority of Otsuka UK. It was not available on the Otsuka Europe or Otsuka UK websites. It appeared to be available in the media section of the Astex website (Astx.com). Otsuka submitted that the matter therefore fell outside the scope of the Code and there was, therefore, no breach of the Code.

The case preparation manager reviewed the initial response and was satisfied that *a prima facie* case had been established and asked for a detailed response.

Otsuka Europe and Otsuka UK provided a joint response and stated that in their view the matter fell outside the scope of the Code. Specifically they noted that Clause 28.2 stated that information or promotional material about medicines which was placed on the Internet outside the UK would be regarded as coming within the scope of the Code, if:

- it was placed there by a UK company/with a UK company's authority, or
- it was placed there by an affiliate of a UK company, or with the authority of such a company and it made specific reference to the availability or use of the medicine in the UK.

The press release in question was issued by Astex in the US and Otsuka Pharmaceutical Co Ltd in Japan (Otsuka Japan). It was not issued by Otsuka Europe or Otsuka UK, nor was it approved for issue or authorized by either company. Furthermore, the press releases did not refer to the availability or use of the medicine in the UK. Otsuka Europe and Otsuka UK noted that the complainant questioned the relevance of the press release to a UK audience. As shown by the lack of any mention of use in the UK or European market or relevance of the information to a UK or European audience, in that it made no reference to any intention imminently, or at all, to seek a marketing authorization in Europe and the information about the diseases of relevance to the referenced application to the FDA focused upon US statistics and North American research sites.

Otsuka Europe and Otsuka UK recognised that Astex approached the Otsuka Europe communications team which then liaised with Otsuka UK in relation to the press release and whilst it was placed in Zinc for Otsuka UK examination, and a review initiated, the review was never completed and the press release was not approved by Otsuka UK, hence the companies' position that the piece was not released 'with the authority' of Otsuka UK.

Associated emails between Astex, Otsuka Europe and Otsuka UK and the press release from Zinc with comments were provided.

In light of the above, Otsuka Europe and Otsuka UK reiterated their position that the press release fell outside the scope of the Code. The companies questioned whether it was procedurally fair to ask them to defend the contents of a press release that they neither prepared, issued or authorized and which focused on potential availability of a product in North America rather than Europe.

Whilst the companies maintained that the press release was outside the scope of the Code, they responded to the clauses raised.

Background

Otsuka Europe and Otsuka UK noted that the press release at issue detailed the results of the ASCERTAIN study, a phase III pharmacokinetic equivalence study of ASTX727 (oral cedazuridine and decitabine fixed dose combination) vs IV decitabine in patients with myelodysplastic syndromes (MDS) and chronic myelomonocytic leukaemia (CMML). The primary end point for the study was total 5-day area under the curve (AUC) exposures of decitabine. There were a number of secondary endpoints, including number of patients with adverse events, the severity of adverse events, leukaemia-free survival and overall survival.

Otsuka Europe and Otsuka UK stated that based on the media circuits to which the press release was distributed and the information on research results contained within it, the press release appeared to have been aimed at the public at large.

The allegations in this case appeared to fall into the following categories.

Statements about ASTX727

There were a number of statements in the press release about ASTX727, such as those in relation to the medicine alleviating the burden of IV infusions, survival benefit, the benefit of oral treatment and a low level of gastrointestinal adverse events. Given that the study in question was a pharmacokinetic equivalence study and safety and efficacy were secondary endpoints, Otsuka Europe and Otsuka UK submitted that they were misleading and could not be substantiated, contrary to the requirements of Clauses 7.2 and 7.4. Further, the statement in relation to side effects did not reflect the available evidence, contrary to the requirements of Clause 7.9. In addition, such misleading statements could be considered as promotional claims for a medicine that did not yet have a marketing authorization, contrary to the requirements of Clause 3.1.

With regard to promotion to the public, and encouraging members of the public to ask for a specific medicine, Otsuka Europe and Otsuka UK noted that the requirements of Clauses 26.1 and 26.2 related to medicines that had a marketing authorization, therefore they did not consider that there was any breach of those clauses, should the matter be deemed to fall within the scope of the Code. However, such statements about a medicine in a document aimed at the public would amount to a failure to maintain high standards, contrary to the requirements of Clause 9.1.

With regard to the allegation that the press release was not clear that ASTX727 was an investigational compound, Otsuka Europe and Otsuka UK noted that the bullet points at the

beginning of the press release stated that a new drug application was planned for the end of 2019, it was noted in the body of the press release that ASTX727 was an investigational compound and there was reference to 'regulatory review and approvals'. Thus, the companies submitted, it was sufficiently clear that the medicine was not yet available for use.

Target audience

Otsuka Europe and Otsuka UK noted the complainant's reference to US epidemiological data and that the study in question was conducted in the US and was not relevant to a UK audience. However, although the press release was primarily concerned with developments in North America, Otsuka Europe and Otsuka UK submitted that the inclusion of such US focused data did not necessarily mean that the press release would not be of interest to a non-US audience. Nevertheless, the companies noted that the audience for the press release was the public at large and the medical language used within it was not easily understood by such an audience, thus the content of the press release was not something that the UK public could reasonably be assumed to need or have an interest in, contrary to the requirements of Clause 11.1.

Information about other clinical studies

With regard to the complainant's comment that the press release referred to the evaluation of cedazuridine-decitabine combinations in other trials that were not the subject of the press release, Otsuka Europe and Otsuka UK agreed that reference to studies other than that which was the newsworthy topic of the press release might encourage health professionals to ask questions about such combinations and studies. This could be characterised as a breach of Clause 3.1.

Information about other medicines

With regard to the allegation that reference in the press release to decitabine was misleading in relation to the medicine's indication in the UK, Otsuka Europe and Otsuka UK noted that the press release stated that:

> '*The hypomethylating agents decitabine and azacitidine are effective treatment modalities for hematologic cancers and are FDA-approved for the treatment of higher risk MDS and CMML.'*

Decitabine (brand name Dacogen) was owned by Astex (and therefore indirectly by Otsuka), and Otsuka Pharmaceutical Inc (Otsuka America) was the licensee in the US and Canada. Janssen marketed Dacogen in the EU and many other territories in the rest of world and was Otsuka America's sub-licensee. Therefore, neither Otsuka Europe nor Otsuka UK had any rights to decitabine.

In the UK, the licence for decitabine was for the treatment of adults with newly diagnosed *de novo* or secondary acute myeloid leukaemia (data from the Electronic Medicines Compendium (emc)). Thus Otsuka Europe and Otsuka UK agreed that the press release misled as to the indication of decitabine in the UK and potentially promoted the medicine outside the terms of its marketing authorization, contrary to the requirements of Clauses 7.2 and 3.2.

Given the above, and if the Panel deemed that the press release fell within the scope of the Code, the content of the press release failed to maintain high standards, contrary to the requirements of Clause 9.1. Given the misleading nature of the information within the press release and the broad target audience, the press release might have brought discredit upon,

and reduced confidence in, the pharmaceutical industry, contrary to the requirements of Clause 2.

The companies noted, given the topic at issue in this case, an Astex press release issued on 3 September regarding the orphan designation of ASTX727 by the FDA. This press release was provided to Otsuka Europe for awareness with a US healthcare audience targeted via the Business Newswire. Otsuka Europe and Otuska UK confirmed that given the release was issued solely by Astex, and with a US only target audience, this was outside of the scope for review by Otsuka Europe and Otsuka UK. It had since come to light that Astex had issued that press release to the same UK/Ireland Business Wire as the phase III ASCERTAIN study press release in question in this case.

PANEL RULING

The first matter for the Panel to consider was whether the press release was covered by the Code. The Panel noted the submission from Otsuka Europe and Otsuka UK that the press release was issued by Astex in the US and Otsuka Japan. Otsuka Europe and Otsuka UK did not issue, approve for issue or authorize the press release and there was no mention of use of the medicine in the UK or Europe. However, it was a clearly established principle under the Code that the UK company was responsible for acts and omissions of its overseas affiliates that came within the scope of the Code. If it were otherwise, UK companies would be able to rely on such acts and omissions as a means of circumventing the Code.

The Panel noted that it appeared that the complainant had accessed the press release via cambridgenetwork.co.uk. The Panel noted that the press release was circulated via a third party by Astex Pharmaceuticals Inc which was a wholly owned subsidiary of Otsuka Pharmaceuticals Co Ltd. A list of the third party's circuits for press releases was provided by Otsuka. This included circuits for the UK and Ireland. The Panel noted from the emails provided by Otsuka Europe and Otsuka UK that both were aware that the press release was going to be issued in the UK and Ireland.

The Panel noted the companies' submission that Astex approached Otsuka Europe's communications team which liaised with Otsuka UK and a review of the press release, using Zinc, was initiated. The review, however, was not completed. The Panel queried why this was the case noting that the email communications stated that 'we have to put joint Astex/Otsuka press releases through [Otsuka UK] review if released in the UK'.

The Panel considered that given the circulation to UK outlets via the third party, the press release was covered by the Code. The Panel noted the involvement of Otsuka Europe and Otsuka UK.

The Panel noted that the press release referred to the safety and clinical activity of ASTX727 being similar to that observed in a previous study. It was stated in the press release that the outcome demonstrated that the fixed dose combination enabled '…successful oral delivery of decitabine alleviating the significant burden of five days of monthly IV infusions for patients who might continue to benefit from the drug for several months or even years'. It was further stated that ASTX727 could bring a new treatment option to patients with 'these deadly diseases'. The press release also stated that 'ASTX727 is an investigational compound and is not currently approved in any country'.

The Panel noted Otsuka's submission that although decitabine was licensed in the UK, the combination with cedazuridine (ASTX727) was not and that in the UK decitabine IV was licensed for newly diagnosed, *de novo*, or secondary acute myeloid leukaemia. The Panel also noted that the ASCERTAIN Study was a pharmacokinetic equivalence study and that safety and efficacy were secondary endpoints. The Panel agreed with Otsuka that statements about alleviating the burden of IV infusions, survival benefit, low level of gastrointestinal adverse events and the benefit of oral treatment were thus misleading and not capable of substantiation. The Panel ruled a breach of Clauses 7.2 and 7.4 as acknowledged by Otsuka UK and Otsuka Europe. There did not appear to be clinical evidence to support the claims for ASTX727 and gastrointestinal side effects as required by Clause 7.9. Thus, the Panel ruled a breach of Clause 7.9.

The Panel noted that Clause 26.1 stated that prescription only medicines must not be advertised to the public. Clause 26.2 stated that information about prescription only medicines which was made available to the public either directly or indirectly must be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their health professional to prescribe a specific prescription only medicine.

The Panel noted that ASTX727 was not classified as a prescription only medicine. Clauses 26.1 and 26.2 only applied to prescription only medicines. On this very narrow technical point the Panel ruled no breach of Clauses 26.1 and 26.2. However, the Panel considered that the press release issued to the public promoted an unlicensed medicine which meant that Otsuka high standards had not been maintained; a breach of Clause 9.1 was ruled.

The Panel noted that the complainant questioned the relevance of the press release for a UK audience given that the study was conducted in North America only with no mention of trial or submission in Europe or the UK. The Panel queried whether the press release should have been distributed in the UK given the medicine was not licensed and the indications for the IV formulation of one of its components was different in the UK compared with the US. However, it did not consider that the circumstances necessarily meant that Clause 11.1 had not been followed. The Panel noted Otsuka Europe and Otsuka UK's submission that the inclusion of such US focused data did not necessarily mean that the press release would not be of interest to a non-US audience. On balance the Panel ruled no breach of Clause 11.1 of the Code based on the complainant's narrow allegation.

Given the circumstances the Panel did not consider that the distribution of the press release for an unlicensed medicine in itself meant that that medicine had been promoted. Nor did the Panel consider that the mention of other studies in the clinical programme necessarily promoted the medicine for those indications. It was not unreasonable to give an overview. The Panel noted its rulings above about the content of the press release and in addition considered that some of the language within it was promotional as acknowledged by Otsuka Europe and Otsuka UK. The Panel therefore ruled a breach of Clause 3.1 in relation to ASTX727. Decitabine IV was licensed in the UK albeit for a different indication than that referred to in the press release and therefore the Panel ruled a breach of Clause 3.2.

The Panel considered that high standards had not been maintained with regard to the information about the study outcomes as ruled in breach of the Code above. The Panel therefore ruled a breach of Clause 9.1.

The Panel noted that a breach of Clause 2 was used as a sign of particular censure and was reserved for such use. The Panel considered that the circumstances did not amount to a breach of Clause 2 and ruled accordingly.

Complaint received **17 June 2019**

Case completed **15 May 2020**