

VOLUNTARY ADMISSION BY ASTELLAS EUROPE

Use of withdrawn advertisement

Astellas Pharma Europe (Astellas Europe) voluntarily admitted that an electronic advertisement for Xtandi (enzalutamide) referred to the medicine as 'new' more than 12 months after it was introduced. Xtandi was for use in certain men with metastatic castration-resistant prostate cancer.

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 Astellas Europe.

Astellas Europe explained that Xtandi was approved on 21 June 2013, and the 'new' indication and data referred to in the advertisement at issue related to an extension of indication approved in November 2014.

The detailed response from Astellas Europe is given below.

The Panel noted Astellas Europe's submission that the extended indication referred to in the claim 'new indication' had been available for over 12 months. Thus the Panel ruled a breach of the Code as acknowledged by Astellas Europe.

Similarly, the TERRAIN study (Shore *et al* 2016), described as a new publication, was published in January 2016, more than 12 months before the advertisement which was the subject of the voluntary admission. The Panel considered that the description of the publication as new was misleading and high standards had therefore not been maintained. A breach of the Code was ruled.

As the advertisement, subject to the voluntary admission, had not been certified a further breach of the Code was ruled.

The Panel noted the sequence of events that led to the publication of the advertisement at issue and that fundamental errors had occurred. In certain respects Astellas had been let down by third parties for which it was, nonetheless, responsible under the Code. Nonetheless, Astellas Europe's governance of its agency and control of materials had been poor. High standards had not been maintained. A breach of the Code was ruled. The Panel found it difficult to understand how such errors could occur at a time when compliance at Astellas was under the spotlight with particular reference to Cases AUTH/2780/7/15, AUTH/2883/10/16, AUTH/2939/2/17 and AUTH 2940/2/17. In this environment the Panel considered that the company's failure in 2017 to send any instruction to its agency in relation to the withdrawal of the advertisement certified in June 2016 (ref XTD/15/0027/EU) and to follow the withdrawal/recall process was incomprehensible. In addition, the advertisement subject to the voluntary admission had not been certified. The Panel

considered that the circumstances had brought the industry into disrepute. A breach of Clause 2 was ruled.

Astellas Pharma Europe Limited (Astellas Europe) voluntarily admitted that an electronic advertisement for Xtandi (enzalutamide) referred to the medicine as 'new' more than 12 months after it was introduced. Xtandi was for use in certain men with metastatic castration-resistant prostate cancer.

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 Astellas Europe.

VOLUNTARY ADMISSION

Astellas Europe explained that Xtandi was marketed in a number of its European affiliates including the UK. It was initially approved on 21 June 2013, and the 'new' indication and data referred to in the advertisement at issue related to an extension of indication:

'for the treatment of adult men with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.'

The European Commission (EC) decision to approve the extended indication was taken on 28 November 2014, and the new indication was introduced in December 2014, with advertising materials which included the claim 'new indication'.

The TERRAIN study (efficacy and safety of enzalutamide vs bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study) was published in January 2016 (Shore *et al* 2016) and subsequent Xtandi advertisements used the claim 'new publication' to refer to this study.

An Astellas Europe employee saw an advertisement on Medscape for Xtandi in the first weekend in May 2017, and noted that it included the terms 'new indication' and 'new publication'. On the next working day (8 May 2017), the employee informed the HealthCare Compliance team, and an investigation was commenced.

Investigation

A digital advertisement (ref ENZ/14/0077/EUd(1)) was certified in July 2015 which comprised of the following:

- a scrolling leaderboard consisting of four rotating screens to be displayed as a header/footer banner,

- an expanded leaderboard displayed when the user hovered over the scrolling leaderboard, and
- a click through page of advertising plus prescribing information displayed when clicking on the 'click to find out more' or 'Prescribing Information' buttons.

Astellas Europe provided a summary which explained the experience for viewing the advertisement.

The advertisement included a 'new indication' claim to reflect the new indication which was launched in December 2014. These materials were available on two internet-based services which provided scientific literature and medical news to health professionals.

Astellas Europe submitted that, via its third party advertising agency, it provided instructions to cease using the advertisement before the 12-month anniversary of the new indication launch date, and the two internet based services confirmed that it was discontinued in September 2015 although the job bag was not withdrawn in Zinc until 7 September 2016.

A revised advertisement (ref XTD/15/0027/EU) without the 'new indication' claim was certified on 2 June 2016 and was only available on one other site offering the latest medical news and information from 14 June 2016. Again, this comprised of the scrolling header/footer banners, expanded leaderboard and click through page of advertising plus prescribing information. This advertisement referred to the TERRAIN study as a 'new publication'.

In August 2016, when the advertising agency implemented the digital links for the advertisement for mobile devices, it inadvertently provided a link for a different file for the click through page of advertising plus prescribing information (ref XTD/16/0013/APELb). The content and prescribing information were identical, including the claim 'new publication', but the job code and date of preparation were different, and this item was certified for use as a print journal advertisement. Astellas did not know at the time that the incorrect file was used. This was discovered as a result of its investigations in May 2017.

In November 2016, there were technical issues with the display of the scrolling leaderboard. The relevant company sourced what it believed were the same file links via an advertisement server hosted by a third party provider to Astellas' advertising agency. It appeared that old/withdrawn files were still available on the advertisement server and so the company inadvertently linked to one of the withdrawn, out-dated scrolling leaderboard files which included the 'new indication' claim (ref ENZ/14/0077/EUd(1)). Astellas Europe was not told about the technical issue or the actions taken to address this.

Astellas Europe also discovered during the investigation that the advertisement certified for use from June 2016 was automatically withdrawn on its expiry date in Zinc, 1 March 2017. The Astellas recall/withdrawal procedure was not followed, and

therefore its advertising agency was not instructed to withdraw this advertisement.

Astellas Europe had thus concluded that the advertisement consisted of files from three different job bags:

- 1 A scrolling leaderboard file from an old/withdrawn job bag which included the claim 'new indication'. This was visible from November 2016 to May 2017 (ref ENZ/14/0077/EUd(1)).
- 2 Click through page of advertising plus prescribing information, which although with the same content as the item at issue, was certified for a different use. This included the claim 'new publication', referring to data published in January 2016. This was visible from August 2016 to May 2017 (ref XTD/16/0013/APELb).
- 3 A scrolling leaderboard file from the intended advertisement. This job bag was automatically withdrawn in Zinc on its expiry date, 1 March 2017, however the complete Astellas withdrawals procedure was not followed, and hence Astellas Europe's advertising agency was not instructed to remove this advertising at that time. This was visible from June 2016 to May 2017 (ref XTD/15/0027/EU).

Astellas Europe confirmed that all Xtandi advertisements and prescribing information were removed on 8 May 2017. All items were now withdrawn in Zinc, and the complete Astellas recall/withdrawals process was in progress. At no time was incorrect or out-of-date prescribing information available to health professionals.

Agency Oversight

Astellas Europe submitted that as part of the investigation in to these issues, it had reviewed:

- The terms of engagement between it and its advertising agency and the third party used by the advertising agency and compliance to these terms
- Astellas internal supplier vetting procedures.

The advertising agency contract

Astellas Europe stated that it had signed a master services agreement (MSA) with the advertising agency which was effective 13 April 2012 and subsequently extended. This investigation revealed that the MSA had, however, expired in September 2016.

The MSA included clauses intended to ensure that agency personnel were appropriately trained, that Astellas' permission was required to change any project material and that prior written agreement was required from Astellas Europe before the advertising agency could subcontract any activities. The advertising agency had provided evidence of training on the Code delivered in September 2014 and repeated in February 2017. Sections of the contract which dealt with project material, personnel and assignment and sub-contracting were reproduced.

Astellas Europe noted that there was no contractual arrangement between Astellas and the third party used by the advertising agency, and the advertising agency had not requested Astellas' written consent to assign the role of managing the advertisement server for Astellas advertisements to the advertising agency's third party. Until this incident occurred and the resulting investigation was conducted, Astellas Europe did not know about the advertising agency's third party's involvement.

Agency vetting and monitoring

Astellas Europe stated that it now had a process (effective 18 August 2016) whereby third party suppliers were vetted in accordance with its standard operating procedure (SOP), Working with suppliers SOP-1479. This SOP required that a summary of key Astellas Europe SOPs, Rules of Engagement, was sent to all suppliers providing services that fell within the scope of the Code, and certain suppliers were also required to complete a supplier questionnaire designed to elicit information about Astellas Europe key compliance requirements. If this questionnaire was not satisfactorily completed, then further action was taken such as, *inter alia*, training, audits of the supplier or removal from the list of approved suppliers to Astellas.

The advertising agency was provided with the Rules of Engagement and completed the supplier questionnaire; it confirmed that it would comply with the Rules of Engagement in August 2016.

Use of the word 'new' and the withdrawal of materials

Astellas Europe stated that the relevant Astellas SOPs and checklists were reviewed to assess the clarity of instruction provided around managing materials including 'new' claims. The existing recall/withdrawals procedure was also reviewed. The current recall/withdrawals SOP was considered to be robust and clear and no changes would be made. The SOP and checklists concerning the review of materials would be revised to provide more explicit instruction on managing materials including the word 'new'.

In addition, face-to-face training on the 'EHQ [European Headquarters] Review and Approval of Material and Activities' and the 'Material Recall and Withdrawal' SOPs was scheduled through June 2017 for all relevant staff. This training would emphasise the importance of appropriately managing items including the word 'new' and the importance of conducting robust recall/withdrawal of expiring materials.

Relevant clauses

Given the above, Astellas Europe fully accepted that it had breached the following clauses:

Clause 7.11 use of the claim 'new' for a therapeutic indication promoted for more than 12 months, and for a publication greater than 12

Clause 14.1 months after the publication date use of un-certified material (ie material used following withdrawal) and use of material certified for a different purpose.

Conclusion

Astellas Europe submitted that it had taken immediate steps to ensure removal of incorrect material as soon as it was discovered.

Astellas Europe did not consider there was any attempt or intention on its part to use material that was out-of-date, withdrawn, or certified for another purpose, it fully recognised that under the Code it was responsible for its actions whether intentional or not, and for any acts or omissions of its third party suppliers.

Astellas Europe considered that the actions begun following its earlier voluntary admissions to reinforce its process for third party management (Cases AUTH/2912/12/16 and AUTH/2883/10/16) would also help to prevent these mistakes in the future.

Astellas Europe was asked to provide the Authority with any further comments in relation to the requirements of Clauses 2 and 9.1 in addition to Clauses 7.11 and 14.1 as cited by the company.

RESPONSE

Astellas Europe stated that when it made its voluntary admission, the three job bags in question had been withdrawn in Zinc, and the complete recall/withdrawals process was in progress. During the recall of one of the three job bags, further relevant information was discovered.

Astellas Europe explained that the print advertisement that appeared in error (XTD/16/0013/APELb) was part of a family of four identical print advertisement job bags which differed only with respect to the intended journal. All four were recalled together at the end of May 2017. During that process, it was discovered that one of those print advertisements, which included the claim 'new publication' based on a publication from January 2016, appeared in the Journal of Clinical Oncology in January and February 2017 (XTD/16/0013/APELc). The Journal of Clinical Oncology had formally acknowledged that it was instructed verbally and in writing on 4 November 2016 to cancel the advertisement but, in error, it did not do so. Thus, this was regrettably a further example of an advertisement containing a 'new publication' claim to appear more than 12 months after the date of the new publication.

Astellas Europe stated that it had no further comment in relation to Clauses 7.11 and 14.1.

With regard to Clauses 9.1 and 2, Astellas Europe stated that it acted immediately to ensure the removal of incorrect material as soon as it was discovered. Astellas Europe did not consider there

was any attempt or intention on its part to use material that was out-of-date, withdrawn, or certified for another purpose. The company recognised that under the Code it was responsible for its actions intentional or not. In addition, whilst Astellas Europe considered that it was let down by the agency, it had recognised that it remained fully responsible for any acts or omissions of its third party suppliers.

With regard to the print advertisement the completion of the formal recall/withdrawals process revealed that this advertisement ran in error in the journal of Clinical Oncology in January and February 2017. The journal had provided written acknowledgement that it was instructed in November 2016 to cancel the advertisement, but in error it did not do so. However, again Astellas Europe recognised that it remained fully responsible for the acts or omissions of its suppliers.

On reflection, and following discovery of another error during the formal recall/withdrawals procedure, Astellas Europe acknowledged that it had not maintained high standards in relation to control of materials or third party management and had therefore breached Clause 9.1 of the Code.

Given the comments above, Astellas Europe understood that the Panel might wish to consider the requirements of Clause 2 in relation to the lack of control of materials and third party management.

PANEL RULING

The Panel noted Astellas Europe's admission that an advertisement for Xtandi on Medscape which was noticed by an employee on a website offering medical news and information for health professionals during the first weekend in May 2017 included the terms 'new indication' and 'new publication'.

The Panel noted Astellas' submission that a new extended indication for Xtandi was approved in November 2014 and promoted using the claim 'new indication' from December 2014. A digital advertisement (ref ENZ/14/0077/EUd(1)) which included a 'new indication' claim was discontinued in September 2015. (This was not withdrawn in Zinc until 7 September 2016). The Terrain study was published in January 2016. A revised digital advertisement (ref XTD/15/0027/EU) published on the website without the 'new indication' claim referred to the TERRAIN study as a 'new publication' and was certified on 2 June 2016. The Panel noted that there were three distinct parts to the digital advertisement: a scrolling leaderboard comprising four rotating screens, an expanded leaderboard and a click through page of advertising which included prescribing information.

The Panel noted Astellas Europe's submission that the advertisement at issue consisted of files from three different job bags.

In relation to the scrolling leaderboard, the Panel noted Astellas Europe's explanation that in November 2016, due to technical issues with

the display and without reference to Astellas, the publisher had, on its own initiative, linked to a withdrawn and out-of-date scrolling leaderboard file (ref ENZ/14/0077/EUd(1)) which it had discovered on a server hosted by a third party provider to Astellas Europe's advertising agency. This withdrawn file included the 'new indication' claim. This out-of-date scrolling leaderboard was visible as part of the advertisement at issue from November 2016 to May 2017.

In relation to the click-through page of advertising and prescribing information, in August 2016 when Astellas Europe's agency implemented the digital links for the advertisement for mobile devices, it inadvertently provided a file that was certified for use as a print journal advertisement (ref XTD/16/0013/APELb). It contained identical content and prescribing information to the intended version, only the job code and date of preparation were different. It included the claim 'new publication'. This was visible as part of the advertisement at issue from August 2016 to May 2017.

The balance of the advertisement, the expanded leaderboard, was from the original advertisement (ref XTD/15/0027/EU) referred to above. It was certified on 2 June 2016 and referred to the 'new publication'. This job bag was automatically withdrawn on its expiry date in Zinc (1 March 2017) but the Astellas recall/withdrawal procedure was not followed and therefore its agency was not instructed to withdraw the advertisement from Medscape. It was visible as part of the advertisement at issue from June 2016 to May 2017.

The Panel noted that Clause 7.11 required that the word 'new' must not be used to describe any product or presentation which had been generally available, or any therapeutic indication which had been generally promoted, for more than twelve months in the UK. The Panel further noted Astellas Europe's submission that the extended indication referred to in the claim 'new indication' had been available for over 12 months. Thus the Panel ruled a breach of Clause 7.11 as acknowledged by Astellas Europe.

Similarly, the TERRAIN study (Shore *et al*), described as a new publication, was published in January 2016, more than 12 months before the advertisement which was the subject of the voluntary admission. The Panel noted that Clause 7.11 applied to products, presentations and therapeutic indications. It did not refer to publications. Nonetheless, the Panel considered that the principle was of broader application and the description of the publication as new was misleading and high standards had therefore not been maintained. A breach of Clause 9.1 was ruled.

Overall, the Panel considered that the advertisement subject to the voluntary admission had not been certified and a breach of Clause 14.1 was ruled.

The Panel noted the sequence of events that led to the publication of the advertisement at issue. Fundamental errors had occurred. In certain respects Astellas had been let down by third parties

for which it was, nonetheless, responsible under the Code. For example, its agency had not advised the company about problems with the published scrolling leaderboard and the publisher's access to, and use of, a withdrawn file retrieved from a server hosted by a third party. Nonetheless, Astellas Europe's governance of its agency and control of materials had been poor. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel found it difficult to understand how such errors could occur at a time when compliance at Astellas was under the spotlight with particular reference to Cases AUTH/2780/7/15, AUTH/2883/10/16, AUTH/2939/2/17 and AUTH 2940/2/17. In this environment the Panel considered that the company's failure in 2017 to send any instruction to its agency in relation to the withdrawal of the advertisement certified in June 2016 (ref XTD/15/0027/EU) and to follow the withdrawal/recall process was incomprehensible. In addition, the advertisement subject to the voluntary admission had not been certified. The Panel considered that the circumstances had brought the industry into disrepute. A breach of Clause 2 was ruled.

The Panel noted Astellas Europe's submission that a print advertisement that included the 'new publication' claim appeared in the Journal of Clinical Oncology in January and February 2017. The Journal of Clinical Oncology formally acknowledged that it was instructed verbally and in writing on 4

November 2016 to cancel the advertisement but did not do so. Whilst Astellas Europe had been let down by the publisher, it was an established principle under the Code that pharmaceutical companies were responsible for third parties even if that third party acted outside the instructions from the pharmaceutical company. The Panel noted that this submission was not the subject of the company's voluntary admission and thus the Panel made no rulings on this matter.

During its consideration of this case the Panel was concerned to note that the advertisement intended for use on the site containing medical news and information for health professionals from June 2016 (ref XTD/15/0027/EU), which included the claim 'new publication', was automatically withdrawn on its expiry date in Zinc (1 March 2017), despite the company acknowledging that it instructed the Journal of Clinical Oncology to cancel the print version of the advertisement in November 2016. It appeared that this advertisement and the three job bags which comprised the advertisement subject to the voluntary admission were only recalled at the end of May 2017. The Panel requested that Astellas Europe be advised of its concerns.

Voluntary admission received **23 May 2017**

Case completed **17 July 2017**