CASE AUTH/2263/9/09

BRISTOL-MYERS SQUIBB v BOEHRINGER INGELHEIM

Viramune journal advertisement

Bristol-Myers Squibb complained about a journal advertisement for Viramune (nevirapine) placed by Boehringer Ingelheim in HIV Medicine, July 2009. Viramune was indicated in combination with other anti-retroviral medicines for the treatment of HIV-1 infected adults, adolescents and children. The recommended dose of Viramune in patients aged 16 years or over was 200mg daily for the first two weeks followed by 200mg twice daily thereafter.

The advertisement stated 'Have you heard?' Followed by 'New Viramune data will be coming soon'. Subsequent text referred to the ArTEN study and briefly described the treatment regimens used. No doses were stated. The text concluded with 'With results expected soon, you will have more reasons than ever to talk about Viramune'. Bristol-Myers Squibb considered that the advertisement encouraged readers to review the results of the ArTEN study when they became available.

Bristol-Myers Squibb noted that ArTEN included, *inter alia*, two Viramune treatment arms, 200mg twice daily (licensed dose) or 400mg once daily (unlicensed dose), each combined with Truvada. As Viramune was not licensed for once daily use, Bristol-Myers Squibb alleged that the advertisement was not in accordance with the Viramune marketing authorization.

Bristol-Myers Squibb also alleged that the advertisement was a 'teaser' in that it elicited an interest in the study's results which would follow without actually providing any information about them.

The detailed response from Boehringer Ingelheim is given below.

The Panel noted that from the overview of the ArTEN study published in 2009 (Soriano and de Rossi), it was clear that some patients would be randomised to receive Viramune 400mg once daily. The study had commenced in 2006 and the results on the primary endpoint were expected during the first quarter of 2009. The first presentation of the results was scheduled for July 2009. Regular safety reviews had been held. There was no indication in the overview as to whether a separate analysis would be made of the once daily/twice daily dosing of Viramune.

The advertisement drew attention to the ArTEN study trial and would encourage health professionals to look at the trial outcome. The Panel noted that the advertisement had been withdrawn before the publication of the ArTEN results. The advertisement did not refer to any dose of Viramune but it elicited interest in the results of the study. The Panel considered it immaterial that the advertisement did not refer to any results. Merely raising awareness of a specific study would draw attention to it. By noting within the advertisement that the results would soon be available the Panel considered that Boehringer Ingelheim had in effect advertised the outcome of that study. Thus all outcomes would have to be in accordance with the Code and not relate to unlicensed doses. There was a difference between using data from a study which included licensed and unlicensed doses to substantiate a specific, within licence claim, and general use for promotional purposes of a study that used licensed and unlicensed doses.

The Panel considered that given the inclusion of an unlicensed dosing regimen in the ArTEN study the advertisement in effect constituted promotion that was inconsistent with the particulars listed in the Viramune SPC. A breach of the Code was ruled.

The Panel did not consider the advertisement was a teaser as set out in the supplementary information to the Code. Information about Viramune had been provided, including prescribing information.

Bristol-Myers Squibb Pharmaceuticals Limited complained about a journal advertisement (ref NVP3846) for Viramune (nevirapine) placed by Boehringer Ingelheim Limited in HIV Medicine, July 2009. Inter-company correspondence had failed to resolve the matter.

Viramune was indicated in combination with other anti-retroviral medicines for the treatment of HIV-1 infected adults, adolescents and children. The dose of Viramune in children was dependent upon body surface area or body weight. In patients aged 16 years or over the recommended dose was 200mg daily for the first two weeks followed by 200mg twice daily thereafter.

The advertisement stated 'Have you heard?' Followed by 'New Viramune data will be coming soon'. Subsequent text explained that the ArTEN study compared Viramune with atazanavir (Bristol-Myers Squibb's product Reyataz) boosted with ritonavir (Abbott Laboratories' product, Norvir) and on a background of Truvada (fixed dose tenofovir and emtricitabine) (Gilead Sciences' product) in treatment naïve patients. The text concluded with 'With results expected soon, you will have more reasons than ever to talk about Viramune'.

COMPLAINT

Bristol-Myers Squibb considered that the

advertisement encouraged readers to review the results of the ArTEN study when they became available.

Viramune was licensed to be taken twice daily. ArTEN compared atazanavir/ritonavir once daily vs Viramune 200mg twice daily (licensed dose) or 400mg once daily (unlicensed dose), each combined with Truvada. As Viramune did not have a licence for once daily use, Bristol-Myers Squibb alleged that the advertisement was not in accordance with the Viramune marketing authorization in breach of Clause 3.2 of the Code.

In inter-company dialogue Boehringer Ingelheim had acknowledged that once daily Viramune did not have marketing authorization but stated that it was not promoting outside the marketing authorization as no direct reference was made to the once daily information. Boehringer Ingelheim had omitted to state that 188 out of the 376 patients were recruited to the once daily Viramune arm and that these patients contributed to the primary endpoint.

Bristol-Myers Squibb also alleged that the advertisement was a 'teaser' in that it elicited an interest in the study's results which would follow without actually providing any information about them.

In inter-company dialogue Boehringer Ingelheim had stated that the description of patient numbers and treatment groups was sufficient for the advertisement not to be considered a teaser. However, the statements 'Have you heard' and 'results expected soon' suggested that the intent was to advertise that the study results would shortly be available, rather than purely to advertise the data stated within it. Bristol-Myers Squibb alleged a breach of Clause 9.1.

RESPONSE

Boehringer Ingelheim stated that the advertisement at issue was used before the ArTEN data was presented at the 5th International Aids Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention, 19-22 July 2009 and was therefore no longer in use.

The ArTEN study compared three treatment arms: atazanavir/ritonavir once daily, Viramune 200mg twice daily (licensed dose), Viramune 400mg once daily (unlicensed dose). Viramune was combined with Truvada.

The advertisement contained a factual description of the number and type of HIV patients and the treatments used in the study (Viramune and Truvada). It also stated that new results from the study would be available soon. In addition, it included the Viramune brand name, the Viramune ArTEN study name and the prescribing information. The advertisement did not refer to once daily (unlicensed) dosing of Viramune.

As the advertisement notified readers of future data from the ArTEN trial and was used before the IAS Conference, 19 - 22 July 2009, the recruitment data and the contribution of the arms of the study to the primary endpoint would not have been confirmed until presentation of the ArTEN results at the conference. Boehringer Ingelheim therefore believed that it was unfair for Bristol-Myers Squibb to state that 'Boehringer Ingelheim had omitted to state that 188 out of the 376 patients were recruited to the once daily Viramune arm and that these patients contributed to the primary endpoint'. Bristol-Myers Squibb had raised a point that it now knew only to be true after the data had been presented and after the advertisement had been withdrawn.

Whilst Boehringer Ingelheim agreed that Viramune was not licensed for once daily dosing it refuted the suggestion that the advertisement promoted Viramune outside its marketing authorization. Boehringer Ingelheim therefore denied a breach of Clause 3.2.

Boehringer Ingelheim understood that the Code did not preclude the use, in promotion, of data from clinical trials where licensed and unlicensed treatment regimens were included. However, only the data for licensed dosing regimens could be used in promotional material to substantiate claims. Boehringer Ingelheim therefore believed that the ArTEN study could be used in promotion in an appropriate manner. It also believed that the advertisement at issue was an appropriate use of the ArTEN study for the promotion of Viramune.

Boehringer Ingelheim refuted the suggestion that high standards had not been maintained in breach of Clause 9.1. A 'teaser' advertisement was one that elicited an interest in something without providing any information about it. The advertisement clearly provided information about the ArTEN study (factual description of the estimated numbers and type of HIV patients that entered the study and the basic treatment groups evaluated) and a statement that data from the study would be available in the future.

Boehringer Ingelheim understood that the Code did not require that the information provided be about the results as Bristol-Myers Squibb stated in its complaint. Boehringer Ingelheim equally believed that the advertisement did not contain any language to encourage readers to review specifically the results of the study as opposed to the study in its entirety.

Boehringer Ingelheim believed that the advertisement was an appropriate method of increasing clinicians' awareness of an important clinical trial before the results were presented. The ArTEN study provided new important toxicity and safety information for health professionals treating HIV with commonly used treatment regimens under specific therapeutic guidance:

- The European Medicines Evaluation Agency's scientific committee, the Committee for Proprietary Medicinal Products (CPMP) added important CD4+ guidance concerning patient management and risk factors for hepatic and rash reactions to the Viramune summary of product characteristics (SPC) (4 February 2004) which stated that nevirapine should be used only in men <400 cells/mm3; women <250 cells/mm3 unless the benefit outweighed the risk.
- Unlike previous studies, patients enrolled in the ArTEN study had CD4+ cell counts as recommended within the CD4+ guidelines for nevirapine use (men <400 cells/mm3; women <250 cells/mm3). Previous studies had included patients with higher CD4+ counts and thus this was the first study to prospectively evaluate the efficacy and safety of nevirapine use within the CD4+ count guidelines.
- The combination of tenofovir and emtricitabine [Truvada] was recommended as one of the first line treatment options in all major guidelines, and was widely used. It was therefore a treatment option that physicians were likely to consider. ArTEN was the first large study to examine the efficacy and safety of nevirapine in combination with tenofovir and emtricitabine; smaller studies had provided conflicting results.

Since this advertisement clearly provided information about the ArTEN study (ie patient numbers, treatment groups) it therefore, by definition, could not be considered as a 'teaser' advertisement and so did not breach Clause 9.1.

The Authority had requested a copy of the information that would be supplied to a health professional who contacted Boehringer Ingelheim. All responses for further information to this advertisement would be referred to medical information and the response would depend on the specific information being requested. Whilst the advertisement was being used Boehringer Ingelheim would have only been able to respond on request to provide details of the clinical trial design and/or the date when the ArTEN data would be presented.

In response to a request for further information Boehringer Ingelheim stated that the information that was in the public domain about the ArTEN study when the advertisement was published would have been that presented on www.clinicaltrials.gov. In addition, an overview of the ArTEN trail had been published (Soriano and de Rossi, 2009).

The information now in the public domain about the ArTEN study consisted of two poster presentations, one from the IAS Congress, July 2009 (Soriano *et al*) and the other from the 49th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), September 2009 (Johnson *et al*).

In response to the Panel's request for a copy of the further information that would now be supplied to a health professional who contacted Boehringer Ingelheim, the company stated that all requests for further information to the advertisement would be referred to medical information; the response would depend on the specific information requested. Medical information would contact the enquirer to ask which specific information relating to ArTEN was required. If the enquirer requested information on the study design the letter entitled 'ArTEN study design information request' would be provided. If the enquirer specifically requested the data presented on ArTEN to date, then the letter entitled 'request for ArTEN data' would be provided along with the poster publications.

PANEL RULING

The Panel noted that from the overview of the ArTEN study published in 2009 (Soriano and de Rossi), it was clear that some patients would be randomised to receive Viramune 400mg once daily. The study had commenced in 2006 and the results on the primary endpoint were expected during the first quarter of 2009. The first presentation of the results was scheduled for July 2009. Regular safety reviews had been held. There was no indication in the overview as to whether a separate analysis would be made of the once daily/twice daily dosing of Viramune.

The advertisement drew attention to the ArTEN study and would encourage health professionals to look at the outcome. The Panel noted that Boehringer Ingelheim had withdrawn the advertisement before the publication of the ArTEN results. The Panel did not consider that this meant that the advertisement could not be in breach of the Code. The advertisement did not refer to any dose of Viramune but it elicited interest in the results of the study. The Panel considered it immaterial that the advertisement did not refer to any results. Merely raising awareness of a specific study would draw attention to it. By noting within the advertisement that the results would soon be available the Panel considered that Boehringer Ingelheim had in effect advertised the outcome of that study. Thus all outcomes would have to be in accordance with the Code and not relate to unlicensed doses. There was a difference between using data from a study which included licensed and unlicensed doses to substantiate a specific, within licence claim, and general use for promotional purposes of a study that used licensed and unlicensed doses.

The Panel considered that given the inclusion of an unlicensed dosing regimen in the ArTEN study the advertisement in effect constituted promotion that was inconsistent with the particulars listed in the Viramune SPC. A breach of Clause 3.2 was ruled.

The Panel did not consider the advertisement was a teaser as set out in the supplementary information to Clause 9.1. Information about

Viramune had been provided, including prescribing information, and thus the Panel ruled no breach.

During its consideration of this case the Panel noted that in its view any requests for information about the ArTEN study generated by the advertisement could not be considered unsolicited. This meant that responding to such requests could not take the benefit of the exemption to Clause 1.2 as set out in the supplementary information to that clause. The Panel requested that Boehringer Ingelheim be advised of its views in this regard.

Complaint received **9 September 2009**

Case completed **27 October 2009**