ANONYMOUS v BOEHRINGER INGELHEIM

Promotion of Spiriva Respimat

An anonymous, non-contactable general practitioner complained about what a Boehringer Ingelheim representative had said about Spiriva Respimat (tiotropium solution for inhalation) at a lunchtime meeting. The complainant alleged that in response to a query about the respimat device and its association with cardiovascular (CV) events, and without published evidence to support the claim, the representative had described the respimat device as 'perfectly safe'.

The detailed response from Boehringer Ingelheim is given below.

The Panel noted that the parties' accounts differed; it was extremely difficult in such cases to know exactly what had transpired. It was unfortunate that the complainant had provided no details of the time or place of the meeting and could not be contacted. Anonymous complaints were judged on the evidence provided by the parties. A complainant had the burden of proving his/her complaint on the balance of probabilities. The representative assumed to be responsible could not recall a meeting which exactly matched the complainant's description and refuted any allegation that he/she would have described the respimat device as 'perfectly safe'.

The Panel noted that contrary to the complainant's position evidence used to support claims did not need to be published. Substantiation (including unpublished data) for any claim should be provided on request.

The Panel noted that Boehringer Ingelheim had sponsored a study to specifically investigate the CV safety of Spiriva Respimat. It had created material about the study for representatives to use only in response to questions about the CV safety of the respimat device; a leavepiece which described the study design and a briefing document which detailed Wise *et al* (2013) discussing the trial design and rationale. Neither item provided any safety results from the study in advance of their formal publication nor did they suggest that Spiriva Respimat was 'safe' or encourage representatives to describe it as such.

The Panel further noted that the complaint was dated 7 August; the study results however, had been internally embargoed until 9 September, following their official publication on 8 September. Thus when the complaint was written, and presumably when the meeting was held, the representative would not have known the study outcome.

The Panel noted that extreme dissatisfaction was usually required before an individual was moved to complain. The Panel further noted that the complainant had been very specific about what the representative was alleged to have stated about the respimat device. However, on the basis of the information before it the Panel considered that the complainant had not demonstrated that, on the balance of probabilities, the representative had claimed that the respimat device was 'perfectly safe'. No breaches of the Code were ruled. The Panel subsequently ruled no breach of Clause 2.

An anonymous, non-contactable complainant who described him/herself as a '[named county] General Practitioner' was concerned about what a Boehringer Ingelheim Limited representative had said about Spiriva Respimat (tiotropium solution for inhalation) during a lunchtime presentation on Spiriva at his/her practice. Spiriva was also available as inhalation powder delivered via a handihaler device. Both presentations were indicated as maintenance bronchodilator treatment to relieve symptoms of chronic obstructive pulmonary disease (COPD).

COMPLAINT

The complainant submitted that at the meeting he/she had raised the much publicised issues around the respimat device and its association with cardiovascular (CV) events in the context of some of the newer products on the market and the fact that other devices might offer patients a safer option. The complainant submitted that in response the representative told him/her about a new 10,000 patient study which showed that the respimat device was 'perfectly safe', however the study had not yet been published. The complainant was concerned that the representative had conveyed a message of safety with no published evidence to support it. The complainant was not clear about exactly what information could or could not be shared when there was a lack of supporting published evidence but assumed that if a company had encouraged its representatives to claim that a device previously linked with CV safety issues was now safe, it should be able to support that position with the right clinical evidence.

When writing to Boehringer Ingelheim, the Authority asked it to respond in relation to Clauses 7.2, 7.4, 7.9, 15.2, 15.9, 9.1 and 2.

RESPONSE

Boehringer Ingelheim stated that it had thoroughly investigated the allegation but it noted that the complainant had provided limited details; no details of the GP practice or of the meeting date were disclosed. Boehringer Ingelheim submitted that given the complainant's anonymity, it was possible that the conversation described had not taken place in the named county. Given these challenges it was impossible to definitively identify the specific meeting.

Nonetheless, as part of Boehringer Ingelheim's internal investigation, the representative working in the county was questioned but could not recall a meeting that exactly matched that described by the complainant.

Boehringer Ingelheim explained that a retrospective pooled analyses of Spiriva Respimat studies published in 2010 found that Spiriva Respimat was associated with a non-significant numerical increase in all-cause mortality compared with placebo; a post-hoc analysis showed an excess of mortality in patients with known cardiac rhythm disorders. The Spiriva Respimat summary of product characteristics (SPC) was accordingly updated. In November 2010, a Drug Safety Update bulletin from the Medicines and Healthcare Products Regulatory Agency (MHRA) highlighted these changes and the reason for them.

Many health professionals were therefore aware of these safety concerns, and the topic was not infrequently raised with Boehringer Ingelheim representatives, including questions about any further action Boehringer Ingelheim was taking to clarify these safety concerns.

To further investigate concerns about the cardiovascular safety of Spiriva Respimat, Boehringer Ingelheim sponsored a phase IV study 'Tiotropium Safety and Performance in Respimat' (TioSPIR) which compared the efficacy and safety of Spiriva Respimat vs Spiriva Handihaler. The study had recently concluded and the abstract was posted online by the New England Journal of Medicine on 31 August 2013; the formal results would be officially announced at the European Respiratory Society (ERS) annual meeting in September 2013. The results of the TioSPIR study were internally embargoed by Boehringer Ingelheim until their official publication and had not been given to any representatives.

During questioning the representative acknowledged that a discussion initiated by a health professional regarding the cardiovascular safety of Spiriva Respimat might have prompted discussion about TioSPIR.

The representative stated that he/she would have stated that the TioSPIR study enrolled over 17,000 patients rather than the 10,000 referred to by the complainant; he/she refuted any allegation that he/she would have stated that the study showed that the respimat device was 'perfectly safe'.

The only Boehringer Ingelheim materials (copies provided) that directly related to the TioSPIR study were:

- a leavepiece which described the TioSPIR study design (ref UK/SPI – 121655). This had recently been discontinued and was withdrawn from use in August 2013.
- a briefing document for the sales teams which gave details of a recent journal publication discussing the TioSPIR trial design and rationale (ref UK/RESP – 131087).

Both of these items were intended for reactive use only, to enable representatives to respond to specific queries about Boehringer Ingelheim's plans to obtain further clinical evidence about the safety of Spiriva Respimat, in particular whether it was associated with increased cardiovascular events.

The briefing document clarified the background and rationale for the TioSPIR study; it stated that 'In a retrospective pooled analysis of Respimat studies a numeric increase in all cause mortality was seen; the excess in mortality was observed in patients with known cardiac rhythm disorders. There was no clear rationale for this difference in mortality outcomes' and continued '… [therefore] there was a need to conduct a mortality driven endpoint trial comparing the two inhaler formations [sic].'

Both the leavepiece and the briefing document outlined the factual design of the TioSPIR study with no indication of any safety or efficacy results in advance of the formal published evidence; and there was no suggestion in either that the study showed that the Spiriva Respimat device was 'safe' nor was there any recommendation for representatives to use that term in relation to Spiriva Respimat promotion.

Boehringer Ingelheim provided the briefing material relating to the potential CV safety concerns associated with Spiriva Respimat (ref SPI/SPV 2709) which was sent to representatives in relation to the MHRA Drug Safety Update bulletin in November 2010, described above.

The briefing material did not emphasise that the Spiriva Respimat device was 'safe' nor was there any recommendation for representatives to use that term in relation to Spiriva Respimat. The emphasis was on the existing efficacy and safety profile of Spiriva in general and only passing reference was made to the TioSPIR study that would 'provide further data to enhance our understanding of the efficacy and safety of Spiriva Respimat'.

In summary, Boehringer Ingelheim could not definitively confirm the details of the complaint given the complainant's anonymity, the lack of specific information about the general practice involved and the date the alleged conversation took place. Boehringer Ingelheim submitted that it took its responsibility only to promote its medicines ethically very seriously and it refuted any allegation that it encouraged its representatives to give a message that a device, previously linked with CV safety issues, was now 'safe' based on unpublished data. Boehringer Ingelheim considered that it had provided appropriate materials and briefings for its representatives to use reactively given the potential interest in the TioSPIR data and public scrutiny of the CV risk profile of Spiriva Respimat.

Boehringer Ingelheim did not consider that there was any evidence that it had encouraged its representatives to provide misleading information about the safety of Spiriva Respimat, or encouraged the inappropriate use of the word 'safe'.
In conclusion, Boehringer Ingelheim denied any breach of Clauses 7.2, 7.4, 7.9, 15.2, 15.9, 9.1 and 2. Boehringer Ingelheim refuted the complainant's allegations, and hoped that the documents provided to the PMCPA demonstrated that high standards

in relation to the promotion of Spiriva had been maintained.

In response to a request for further information Boehringer Ingelheim submitted that the TioSPIR leavepiece (ref UK/SPI – 121655) was created to form a framework for its representatives to reactively respond to queries from health professionals about what actions Boehringer Ingelheim was taking to clarify safety concerns regarding Spiriva Respimat. The representatives could therefore have only discussed information shown in the leavepiece; an overview of the study design which was freely available in the public domain at the time via clinicaltrials.gov. In addition, as stated above, Boehringer Ingelheim submitted that its representatives were subsequently provided with a briefing document about Wise *et al* (2013) which discussed the TioSPIR trial design and rationale (ref UK/RESP – 131087).

The results of the TioSPIR study were embargoed by Boehringer Ingelheim until they were officially published at the ERS annual meeting on 8 September 2013. The Boehringer Ingelheim representatives were informed of the results on 9 September.

Boehringer Ingelheim stated that when the meeting in question was held, presumably some time before 7 August when the complaint was written, no Boehringer Ingelheim representative would have been able to discuss the efficacy or safety results of the TioSPIR study as they were not available to them. The representatives would only have discussed the information available to them in the previously mentioned leavepiece and briefing document. Any additional queries about TioSPIR would have been directed to the medical information team as per their normal practice.

The leavepiece was circulated for use following the annual sales conference in January 2013 and was intended for reactive use only when health professionals queried the safety of Spiriva Respimat and asked what Boehringer Ingelheim was doing to clarify these safety concerns. The instructions for the leavepiece's use were given verbally by the scientific advisor on 31 January and to his/her recollection the briefing was as follows:

> 'The Spiriva sales team was informed of the medico-marketing campaign for Spiriva for 2013. They were informed that similar to previous years, Spiriva Respimat was to be promoted as another device option alongside Spiriva HandiHaler and the topic of Spiriva Respimat safety should only be discussed reactively until TioSPIR results were published in Q3 2013. The sales team were reminded that the ongoing TioSPIR trial was a ~17,000 patient trial comparing tiotropium via the HandiHaler device to tiotropium via the respimat device. In addition, the sales team were informed that that they were permitted to mention the TioSPIR trial only if they were asked by a customer what Boehringer Ingelheim were doing to address the safety concerns about Spiriva Respimat. [This advice followed the publication of media articles expressing concern about the cardiovascular safety of Spiriva Respimat which appeared in UK medical journals in December 2012].
>
> The sales team were informed about a TioSPIR leavepiece in development which was designed to support reactive conversations about the methodology and trial design of the TioSPIR trial. The information contained within this leavepiece was in the public domain at the time through the clinicaltrials.gov website. The sales team were reminded that the results of the TioSPIR study were anticipated to be available in Q3 2013'.

Boehringer Ingelheim noted that the Panel had noted that according to the certificate for the TioSPIR study design leavepiece its intended use was '…to allow sales teams to discuss the study with their customers to help instil confidence in the safety of the brand'. Boehringer Ingelheim clarified that the intention of the TioSPIR discussions was not to indiscriminately nor irresponsibly 'instil confidence in the safety of the brand' but to provide factual information on a reactive basis about the rationale for the TioSPIR study to further investigate the efficacy and safety of Spiriva Respimat.

Boehringer Ingelheim submitted that as previously mentioned, this information would have only been provided when health professionals queried the safety of Spiriva Respimat on a background of ongoing debate in the scientific literature and medical press, and only when health professionals asked what Boehringer Ingelheim was doing to clarify those concerns.

PANEL RULING

The Panel noted that the parties' accounts differed; it was extremely difficult in such cases to know exactly what had transpired. It was unfortunate that the complainant had not provided details of the GP practice nor the date on which the meeting at issue had taken place. The complainant was non-contactable and so the Panel could not ask him/her for more information. Anonymous complaints were judged on the evidence provided by the parties. A complainant had the burden of proving his/her complaint on the balance of probabilities. The Panel noted that the complainant had alleged that in response to a query regarding the respimat device and its association with CV events, the representative had told him/her about a new 10,000 patient study which showed that the respimat device was 'perfectly safe' despite the study not yet being published. The representative assumed to be responsible could not recall a meeting which exactly matched the complainant's description. The representative stated that, if asked he/she would have stated that the TioSPIR study enrolled over 17,000 patients rather than the 10,000 referred to by the complainant; he/she refuted any allegation that he/she would have stated that the study showed that the respimat device was 'perfectly safe'.

The Panel noted that contrary to the complainant's position, evidence used to support claims did not

need to be published. Substantiation (including unpublished data) for any claim should be provided at the request of a health professional or appropriate administrative staff.

The Panel noted Boehringer Ingelheim's submission that many health professionals were aware of the safety concerns associated with Spiriva Respimat and the topic was not infrequently raised with its representatives including questions about any further action Boehringer Ingelheim was taking to clarify those concerns.

The Panel noted that Boehringer Ingelheim had created two items related to the TioSPIR study for reactive use by its representatives in response to questions about the CV safety of the respimat device; a leavepiece which described the study design and a briefing document which detailed Wise *et al* (2013) discussing the trial design and rationale. The Panel noted that neither item provided any safety results from TioSPIR in advance of their formal publication nor did they suggest that Spiriva Respimat was 'safe' or encourage representatives to describe it as such.

The Panel further noted that the complaint was dated 7 August; the TioSPIR study results however, had been internally embargoed until 9 September, following their official publication at the ERS annual meeting on 8 September. Thus when the complaint was written, and presumably when the meeting was held, the representative would not have known the study outcome.

The Panel noted that extreme dissatisfaction was usually required before an individual was moved to complain. The Panel further noted that the complainant had been very specific about what the representative was alleged to have stated about the respimat device. However, on the basis of the information before it the Panel considered that the complainant had not demonstrated that, on the balance of probabilities, the representative had claimed that the respimat device was 'perfectly safe'. The Panel ruled no breach of Clauses 7.2, 7.4, 7.9, 15.2 and 15.9 of the Code. The Panel subsequently ruled no breach of Clauses 9.1 and 2.

Complaint received **7 August 2013**

Case completed **2 October 2013**