CASE AUTH/2757/5/15

ANONYMOUS v BOEHRINGER INGELHEIM

Congress stand presentation

An anonymous, non-contactable complainant alleged that data within a presentation hosted by Boehringer Ingelheim on its stand at a European stroke congress held in the UK, was misleading and not in patients' best interests.

Boehringer Ingelheim marketed Pradaxa (dabigatran) a non-vitamin K antagonist oral anticoagulant (NOAC) indicated, *inter alia*, for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors such as prior stroke, transient ischemic attack, heart failure, diabetes mellitus and hypertension.

The complainant stated that the presentation discussed the relative merits of different dosage regimes for novel anticoagulants and notably the advantages of Pradaxa. Slide 16 was headed 'Consequences of a missed dose' and compared once-daily dosing with twice-daily dosing for a medicine with a half-life of 12 hours and T_{max} of 3 hours. The footnote stated 'AF, atrial fibrillation; BD, twice daily; NOAC, non-vitamin K antagonist oral anticoagulant; OD, once daily'. This was followed by two references, Vrijens and Heidbuchel (2015) and Nagarakanti *et al* (2008). Vrijens and Heidbuchel seemed to be a secondary reference taken from a primary publication Comté *et al* (2007). Graph C in Figure 2 in Vrijens and Heidbuchel was based on Figure 2 of Comté *et al*.

The complainant noted that Comté *et al* reported mathematical modelling of data for antiretroviral agents. The complainant considered that the extrapolation of conclusions based on modelling of data from these agents in a different patient group to cardiovascular patients treated with an entirely different class of medicine was highly questionable. Furthermore the graph presented differed from those in Vrijens and Heidbuchel and Comté *et al* in that it included the half-life of dabigatran and not the half-lives for lopinavir and ritonavir.

The detailed response from Boehringher Ingelheim is given below.

The Panel noted slide 13 raised the question what if a patient had been treated with a NOAC for stroke prevention in atrial fibrillation rather than a vitamin K antagonist and whether thrombolysis was an option. Slide 14 referred to low rates of ischaemic stroke in NOAC trials and showed that the lowest rates were in dabigatran 150mg and 110mg. Slide 15, headed 'Thrombolysis can be considered in a patient on a NOAC if anticoagulant activity can be ruled out', stated that the patient had missed a morning dose of a once-daily NOAC. This meant that IV thrombolysis could still be considered. The slide in question, slide 16, featured a graph which compared concentration when a dose was delivered once- and twice-daily with missed doses on day 7. Slide 17 was headed 'Thrombolysis can be considered in a patient on a NOAC if anticoagulant activity can be ruled out' and asked whether the coagulation assays had ruled out anticoagulant activity. Subsequent slides mentioned dabigatran favourably.

The Panel considered that slide 16 was not clear. Its position between two slides that referred to the clinical use of NOACs, together with the lack of clear labelling meant it was extremely difficult to understand the full context of the graph on slide 16 which had been adapted from Figure 2C of Vrijens and Heidbuchel. The Panel did not accept Boehringer Ingelheim's submission that all the assumptions for Figure 2 in Vrijens and Heidbuchel were clear on slide 16. It was not clear that the graph on slide 16 was a simulation showing a theoretical pharmacokinetic profile for a medicine with a half-life of 12 hours similar to NOACs rather than clinical data on patients taking NOACs. Nor was it clear that the graph was adapted from Figure 2C of Vrijens and Heidbuchel which was headed '1 missed QD [once-daily] dose equals 3 missed BID [twice-daily] doses'. The Panel agreed with Boehringer Ingelheim that Figure 2C in Vrijens and Heidbuchel referred to a simulation similar to what might be expected with NOACs and not to the data in Comté *et al* which was a simulation of data for HIV patients. It appeared that the difference in the half-life of NOACs (around 12 hours) and protease inhibitors (lopinavir/ritonavir 10.7hrs) had been taken into account in Figure 2C.

The Panel considered that slide 16 was misleading as it was not clear that it was simulated data. Its positioning within a promotional presentation for dabigatran together with the footnote did not help the audience understand that it was simulated data and the relevance to the clinical situation was unclear. Whilst the complainant had clearly been misled he/she was incorrect as the simulation was not of HIV patients. The Panel ruled a breach of the Code in relation to the presentation of the simulated data. The Panel noted that the graph on slide 16 was misleading and in addition did not make it clear that it was adapted from Vrijens and Heidbuchel. A breach of the Code was ruled.

With regard to the allegation that HIV data was not relevant to NOACs, the Panel ruled no breach of the Code as slide 16 was not the HIV patient data and thus it was not misleading to omit the half-lives for two HIV medicines, lopinavir and ritonavir.

An anonymous, non-contactable complainant complained about a slide within a presentation (ref UK DBG-151019b) hosted by Boehringer Ingelheim

Limited on its stand at the European Stroke Organisation Congress which was held in Glasgow, 17-19 April 2015.

The slide in question, slide 16, was provided with Boehringer Ingelheim's response. It was headed 'Consequences of a missed dose' and compared once-daily dosing with twice-daily dosing for a medicine with a half-life of 12 hours and T_{max} of 3 hours. The footnote stated 'AF, atrial fibrillation; BD, twice daily; NOAC, non-vitamin K antagonist oral anticoagulant; OD, once daily'. This was followed by two references Vrijens and Heidbuchel (2015) and Nagarakanti *et al* (2008).

Boehringer Ingelheim's product Pradaxa (dabigatran) was a non-VKA (vitamin K antagonist) oral anticoagulant (NOAC). Pradaxa's indications included the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors such as prior stroke, transient ischemic attack, heart failure, diabetes mellitus and hypertension.

COMPLAINT

The complainant stated that the presentation discussed the relative merits of different dosage regimes for novel anticoagulants and notably the advantages of that for Pradaxa. During the discussion a slide entitled 'Consequences of a missed dose' was presented [slide 16].

The complainant stated that the references cited on the slide included Vrijens and Heidbuchel and that having read that paper it seemed to be a secondary reference taken from a primary publication ie Comté *et al* (2007). The graph C in Figure 2 in Vrijens and Heidbuchel was based on Figure 2 of Comté *et al*.

The complainant noted that Comté *et al* reported mathematical modelling of data for antiretroviral agents. The complainant considered that the extrapolation of conclusions based on modelling of data from these agents in a different patient group to cardiovascular patients treated with an entirely different class of medicine was highly questionable. Furthermore the graph presented differed from those in Vrijens and Heidbuchel and Comté *et al* in that it included the half-life of dabigatran and not the half-lives for lopinavir and ritonavir. This misled clinicians and the complainant did not consider that it was in the best interests of patients.

When writing to Boehringer Ingelheim, the Authority asked it to respond in relation to Clauses 7.2 and 7.8.

RESPONSE

Boehringer Ingelheim submitted that the presentation in question was delivered by a professor of neurology with expertise in stroke. The presentation took place from the Boehringer Ingelheim promotional stand located in the area of all other pharmaceutical company exhibition stands. The projector screen faced into the exhibition area. All entry into the exhibition area was through security staff who checked congress badges so that only health professionals registered for the meeting had access to the stands and could have seen the presentation.

Boehringer Ingelheim stated that there was no restriction on who viewed it within the exhibition hall. There were a number of seats on the stand and nearby, otherwise there was room around and between stands from where people could watch the session, although the further away you were, perhaps the sound quality and the visibility of the details on the screen might have been diminished, as one would expect. Only one presentation took place at 10am on Saturday, 18 April 2015 with the opportunity for questions and answers at the end. Boehringer Ingelheim submitted that it did not keep a record or request completion of a registration form from attendees due to the open and fluid nature of the surroundings.

A copy of the presentation was provided showing that of the twenty-three slides presented, slide 16 was the one referred to by the complainant.

The title of the presentation was 'Acute ischaemic stroke in a patient with NVAF [non-valvular atrial fibrillation]: what now?'. The aim of the talk was to discuss the evidence and guideline recommendations for the management of patients with non-valvular atrial fibrillation, already receiving anticoagulant therapy who might then present with an acute ischaemic stroke. Acute treatment of stroke and secondary prevention of stroke were covered in the talk. This was an area of considerable focus currently and the topics covered were very common questions from this clinical community. Using a patient case, the topics of diagnostics, risk factors for stroke, interventional and medicinal therapies were covered. As the talk was about how to manage patients already on anticoagulation the first scenario presented was for a patient receiving warfarin, but with a subtherapeutic (low) INR [international normalised rate]. Reasons for this were discussed and the evidence and guidelines on whether to administer thrombolysis in this setting discussed. As warfarin was not the only anticoagulant available, the next scenario covered was how this management would change if the patient was receiving a NOAC. The next part of the talk went on to discuss questions and blood tests that would be useful in assessing the patient's suitability for thrombolysis. As with the example of the patient on warfarin, non-adherence to medicines was covered here too. As all NOACs had a relatively shorter half-life than warfarin (approximately twelve hours vsforty hours) the slide in question 'Consequences of a missed dose' was very relevant and important to the educational content. Adherence to this class of medicine with a short half-life had caused physicians much concern. Boehringer Ingelheim submitted that the slide in question shown in this context was entirely appropriate and not misleading. The presenter then discussed the evidence and guideline recommendations for how to manage the patient's secondary stroke prevention in light of the preceding events.

The slide mentioned by the complainant (slide 16) contained a graph taken from Vrijens and Heidbuchel. This was cited as the reference on the slide itself. Vrijens and Heidbuchel was about the importance of patient's adherence to short half-life medication and the consequences of failing to adhere. Within the section 'Superior therapeutic coverage with twice-daily dosing regimens' on page 5, the authors gave examples of two medicines (protease inhibitors for which Comté *et al* was cited as a reference, and platelet inhibitors) and from two different patient populations. These formed the basis of the theory and reasons why the authors went on to do their own simulation work.

The next section of Vrijens and Heidbuchel, titled 'A simulation of the consequences of non-adherence with once- or twice-daily dosing' was not referenced to Comté *et al* and contained four graphs in Figure 2 representing the authors own simulations.

The graph in question was C in Figure 2 and was used on slide 16 of the presentation. Boehringer Ingelheim submitted that there was a very clear explanation with the figure explaining the assumptions and background to the graphs. It stated 'These graphs illustrate the theoretical pharmacokinetic profiles of a dose X administered once-daily (QD), and a dose X/2 administered twice-daily (BID), for a drug with a half-life of about 12 h and a T_{max} of 3 h'. Since the graph illustrated the theoretical pharmacokinetic profiles of a dose X QD and a dose X/2 BID for 'a' medicine with half-life of twelve hours and a T_{max} of three hours, it did not refer to lopinavir or ritonavir. Boehringer Ingelheim noted that lopinavir and ritonavir in fact had different half-lives.

Boehringer Ingelheim submitted that all these assumptions explained above were clear on the graph in slide 16. Nothing in the graph presented suggested that it referred to dabigatran. Again, as this represented hypothetical medicines X and X/2 there had been no suggestion or implication on Boehringer Ingelheim's part or the author's part that this was the concentration of dabigatran or in fact lopinavir and ritonavir, which in fact had different half-lives.

The description for graph C in Figure 2 of Vrijens and Heidbuchel stated 'The pharmacological equivalent of missing a single dose in a once-daily regimen (blue dot) is missing three doses (red dots) of a twice-daily dosing regimen'. This explanation had been illustrated by the blue and red dots on slide 16. Boehringer Ingelheim amended the title slide as using the original description based on author's text in the setting of a promotional stand could be misconstrued.

Boehringer Ingelheim strongly contested the statement that the graph had been taken from Comté *et al* and the citation was therefore a secondary data source. Boehringer Ingelheim strongly contested the statement that the graph was used to deliberately mislead clinicians as it considered that it had accurately represented and correctly referenced the graph's source.

Boehringer Ingelheim could, however, see the similarities in shape to the graph in Comté *et al*. However this was not surprising given that pharmacokinetic principles applied to all medicines. In fact it was very clear from this graph that there was a medicine concentration on the y-axis and in the description and assumptions supporting this figure in the paper.

In summary, Boehringer Ingelheim strongly denied either deliberately or unintentionally misleading clinicians as to the source data presented (Clause 7.2) on the congress stand. Boehringer Ingelheim believed it had demonstrated above that it had been mindful of presenting graphs in a clear and balanced way (Clause 7.8) relevant to the overall scientific content of the presentation.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable. Such complaints were accepted and, like all complaints, judged on the evidence submitted by the parties. The complainant had the burden of proving his/her complaint on the balance of probabilities.

The Panel examined the presentation used at the Boehringer Ingelheim exhibition stand. The material related to treating a patient who had had an ischaemic stroke and was taking warfarin for stroke prevention in atrial fibrillation (AF). Slide 13 raised the question what if the patient had been treated with a NOAC for stroke prevention in AF rather than a vitamin K antagonist and whether thrombolysis was an option. Slide 14 referred to low rates of ischaemic stroke in NOAC trials and showed that the lowest rates were in dabigatran 150mg and 110mg. Slide 15 was headed 'Thrombolysis can be considered in a patient on a NOAC if anticoagulant activity can be ruled out' and stated that the patient had missed a morning dose of a once-daily NOAC. This meant that IV thrombolysis could still be considered. The slide in question, slide 16, was headed 'Consequences of a missed dose'. It featured a graph which compared concentration when a dose was delivered once- and twice-daily with missed doses on day 7. Slide 17 was headed 'Thrombolysis can be considered in a patient on a NOAC if anticoagulant activity can be ruled out' and asked whether the coagulation assays had ruled out anticoagulant activity. Subsequent slides mentioned dabigatran favourably.

The Panel examined Vrijens and Heidbuchel which looked at NOACs and considerations of once-daily vs twice-daily regimens and the potential impact on medication adherence. NOACs were said to have plasma half-lives of around 12 hours. This meant that anticoagulation effect declined radically when doses were missed. The paper stated that a twice-daily regimen was less prone than the once-daily regimen to hazardously high peaks or hazardously low troughs in anticoagulation concentration. The paper referred to Comté *et al* which suggested (model based finding) superior therapeutic coverage with twice-daily compared with once-daily protease inhibitors for treating HIV patients. The paper also referred to the superior inhibition (model based

simulation) of platelet aggregation with twice-daily administered ticagrelor compared with a once-daily clopidogrel (Vrijens *et al* 2014).

Comté *et al* stated that the more important factor was maintenance of therapeutic levels of drug action not the concentration in the plasma.

Vrijens and Heidbuchel stated that these two examples showed that while once-daily dosing might be seen as an option to simplify the dosing regimen and increase patient adherence, it might require near-perfect adherence to achieve its intended pharmacodynamic and clinical results, whereas twice-daily dosing depending on the medicine's pharmacokinetics, was more forgiving of variations in dose-timing or occasionally missed doses. The real therapeutically relevant question was the impact of suboptimal adherence on the pharmacologic effects of the medicine.

Vrijens and Heidbuchel further stated that it was of paramount importance to investigate these elements also in detail in NOAC patients, as the consequences of suboptimal pharmacologic effects were so severe (bleeding or thrombotic events, both of which might be fatal). Clearly, the above-mentioned findings could not be just extrapolated to NOAC therapy; not only might the consequences of non-adherence differ depending on the specific characteristics of the medicine but also the patients taking NOACs were different from those taking HIV medication and might therefore have specific issues.

The graph in question, slide 16, was taken from Figure 2C of Vrijens and Heidbuchel which was a simulation to depict the typical pharmacokinetic profile for a medicine with a half-life of about 12 hours, similar to NOACs. The graph in question showed that the pharmacological equivalent of missing a single dose in a once-daily regimen was missing three consecutive doses of a twice-daily dosing regimen.

Vrijens and Heidbuchel stated that the findings from the simulation of the consequences of non adherence with once- or twice-daily dosing showed the importance of considering a twice-daily dosing regimen instead of automatically assuming that once-daily dosing would be better due to the higher percentage of doses taken. It should also be clear that there would not be one all-encompassing answer on which dosing regimen was best for NOACs; this question needed to be assessed for each NOAC and each patient separately. It remained to be proven how far these projected differences also reflected clinical outcomes with NOACs.

The Panel considered that there were two aspects to the complaint. Firstly, whether using the modelling data was misleading *per se* and secondly, whether using simulated data from one patient group in relation to a different patient group was also misleading.

The Panel considered that slide 16 was not clear. Its positioning in the presentation between two slides that referred to the clinical use of NOACs, together with the lack of clear labelling meant it was extremely difficult to understand the full context of the graph on slide 16 which had been adapted from Figure 2C of Vrijens and Heidbuchel. The Panel did not accept Boehringer Ingelheim's submission that all the assumptions for Figure 2 in Vrijens and Heidbuchel were clear on slide 16. It was not clear that the graph on slide 16 was a simulation showing a theoretical pharmacokinetic profile for a medicine with a half-life of 12 hours similar to NOACs rather than clinical data on patients taking NOACs. Nor was it clear that the graph on slide 16 was adapted from Figure 2C of Vrijens and Heidbuchel which was headed '1 missed QD dose equals 3 missed BID doses'. The Panel agreed with Boehringer Ingelheim that Figure 2C in Vrijens and Heidbuchel referred to a simulation similar to what might be expected with NOACs and not to the data in Comté *et al* which was a simulation of data for HIV patients. It appeared that the difference in the half-life of NOACs (around 12 hours) and protease inhibitors (lopinavir/ritonavir 10.7hrs) had been taken into account in Figure 2C.

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With regard to the allegation that HIV data was not relevant to NOACs, the Panel ruled no breach of Clause 7.2 of the Code as slide 16 was not the HIV patient data and thus it was not misleading to omit the half-lives for two HIV medicines, lopinavir and ritonavir.

Complaint received **8 May 2015**

Case completed **1 July 2015**