CASE AUTH/2026/7/07

CONSULTANT IN ELDERLY/STROKE MEDICINE v BOEHRINGER INGELHEIM

Actilyse press release

A consultant in elderly/stroke medicine alleged that an Actilyse (alteplase) press release, issued by Boehringer Ingelheim, contained inaccurate and misleading claims about safety, outcomes and mortality to the extent that it appeared that alteplase saved lives as mortality was reduced from 17.3% to 11.3%. Such an effectiveness claim and the Department of Health's choice to indicate that thrombolysis reduced death and disability made it appear that alteplase was a life-saving treatment whereas in fact it saved autonomy as trial evidence showed no significant life-saving potential. Furthermore and worse was that Boehringer Ingelheim failed to publicly disclose additional information presented to the National Institute for Health and Clinical Excellence (NICE) ie that in the UK the mortality with alteplase was 20.6% vs 17.3% quoted in its press release. The UK press was misled and misinformed and the evidence was there in the detail but not in plain view on the NICE website to disprove such false promotional claims about the effects of Actilyse. Was Boehringer Ingelheim working to high standards and keeping the industry in a state of good repute and increasing the confidence in the industry to tell the truth about its products in a fair and balanced manner?

The Panel noted that the press release was issued by the UK company's German corporate colleagues and placed on its corporate website. It was an established principle under the Code that UK companies were responsible for the acts/omissions of their overseas affiliates that came within the scope of the Code.

The press release was headed 'Actilyse (alteplase) recommended by [NICE] for treatment of acute ischaemic stroke. NICE Appraisal Committee concludes that alteplase is clinically and cost effective'. Text beneath read 'For medical media, outside the US only'. The press release referred to the UK publication of the appraisal. A quotation from the company read '… we hope that this recommendation from NICE will allow more patients with qualifying stroke in the UK to benefit from treatment with Actilyse'. The penultimate paragraph of the 'Notes to Editor' on the final page of the press release read 'Please be advised. This release is from the Corporate Headquarters of Boehringer Ingelheim and is intended for all international markets. This being the case, please be aware that there may be some differences between countries regarding specific medical information including licensed uses. Please take account of this when referring to the material'. The Panel noted that the UK company had not referred UK doctors or media to the site. The Panel did not know whether the German company had done so. The Panel noted the comments in the press release about the intended audience. Nonetheless the Panel noted that the press release referred to a UK public document and discussed benefit to UK patients. The Panel noted that Boehringer Ingelheim twice referred to it as a press release relating to UK matters and explained that procedures had been put in place to ensure that such releases complied with the Code. The Panel considered that given its content, the press release was subject to the UK Code.

Actilyse was indicated *inter alia* for fibrinolytic treatment of acute ischaemic stroke. The summary of product characteristics (SPC) stated that such treatment must be started within 3 hours of the onset of stroke symptoms and after prior exclusion of intracranial haemorrhage by means of appropriate imaging techniques.

According to the press release NICE had recommended the use of alteplase for the treatment of patients with acute ischaemic stroke. The press release referred to data in the NICE report which, based on a series of trials, demonstrated efficacy for treating acute ischaemic stroke within 3 hours and showed that 'alteplase resulted in significantly better outcomes for patients in terms of death and dependency at 3 months compared with placebo'.

The press release also explained that the NICE appraisal committee had noted independent European data which assessed the safety and efficacy of alteplase in routine clinical practice and showed that mortality rates following alteplase treatment were 'even lower in routine clinical practice than had previously been seen in randomised clinical trials (11.3 percent vs 17.3 percent)'. More information about the data source appeared in the 'Notes to Editor' section.

Section 5.1 of the Actilyse SPC, Pharmacodynamic properties, Acute stroke, referred to two studies where a significantly higher proportion of patients had a good outcome (no/minimal disability) compared with placebo, results which were not confirmed in 3 other studies wherein the majority of patients were not treated within 3 hours of stroke onset. However an analysis of all patients in these studies treated within 3 hours of stroke onset confirmed the beneficial effect of alteplase. The risk difference vs placebo for a good recovery was 14.9% despite an increased risk of severe and fatal intracranial haemorrhage. The data did not allow a

definite conclusion to be drawn on treatment effect on death. Nevertheless overall the benefit/risk of alteplase, given within 3 hours of stroke onset and taking into account the SPC's precautions was considered favourable.

The Panel noted that it was clear from the outset that the press release related to alteplase and treatment of acute ischaemic stroke. It was acceptable to discuss the benefit which might flow from using a medicine for its licensed indication so long as such discussion was placed clearly in the context of the licensed indication and otherwise complied with the Code.

The press release did not state that mortality was reduced from 17.3% to 11.3% as alleged by the complainant. Rather these figures were presented as a comparison of mortality rates seen in routine clinical practice vs randomised clinical trials. The press release made this clear. No breach of the Code was thus ruled on this point.

The Panel noted that the press release discussed mortality data. The Panel noted the SPC statement that the data did not allow a definite conclusion to be drawn on the treatment effect on death. The press release implied that the data in this regard was unequivocal and that was not so in relation to treatment of acute ischaemic stroke. The press release was misleading in this regard and could not be substantiated. Breaches of the Code were ruled.

The Panel considered that given its rulings above high standards had not been maintained regarding the mortality data mentioned in the press release. A breach of the Code was ruled. On balance the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such.

A consultant in elderly/stroke medicine complained about an Actilyse (alteplase) press release issued by Boehringer Ingelheim Limited.

COMPLAINT

The complainant submitted that, in correspondence, Boehringer Ingelheim had stated that it would remove a press release from its website. The complainant alleged that the press release contained inaccurate and misleading claims about safety, outcomes and mortality to the extent that it appeared that alteplase saved lives as mortality was reduced from 17.3% to 11.3%. Such an effectiveness claim and the Department of Health's choice to indicate that thrombolysis reduced death and disability made it appear that alteplase was a life-saving treatment whereas in fact it saved autonomy as trial evidence showed no significant life-saving potential. Furthermore and worse was that Boehringer Ingelheim failed to publicly disclose the additional information presented to the National Institute for Health and Clinical Excellence (NICE) ie that in the UK the mortality with alteplase was 20.6% (UK specific data from the SITS-MOST (Safe Implementation of Thrombolytis in Stroke – MOnitoring STudy) data) and not 17.3% as quoted in the press release. The UK press was misled and misinformed and the evidence was there in the detail but not in plain view on the NICE website to disprove such false promotional claims about the effects of Actilyse. Was Boehringer Ingelheim working to high standards and keeping the industry in a state of good repute and increasing the confidence in the industry to tell the truth about its products in a fair and balanced manner?

When writing to Boehringer Ingelheim, the Authority asked it to respond in relation to Clauses 7.2, 7.4 and 9.1 of the Code in addition to Clause 2 alluded to by the complainant.

RESPONSE

Boehringer Ingelheim explained that NICE had reviewed the data on Actiyse for the treatment of ischaemic stroke and had posted a Final Appraisal Determination on its website on 4 May 2007; appeals had to be submitted in writing by 21 May 2007 but none were received.

A press release was placed on the Boehringer Ingelheim corporate website on 14 May 2007 by the UK company's German colleagues. This press release was stimulated by the appearance of a positive article in Scrip announcing a positive NICE appraisal for the use of Actilyse in acute ischaemic stroke and a statement on the NICE website. Confusion was caused by the terminology 'Final Appraisal Determination' which the corporate colleagues incorrectly interpreted as meaning final approval. As soon as Boehringer Ingelheim in the UK knew of the press release (16 May) it immediately asked Corporate Communications to remove it from the corporate website. This was done within 2 hours.

Boehringer Ingelheim acknowledged that, although the content of the press release was accurate, it should not have been posted on the corporate website in advance of the release by NICE of the finally approved single technology appraisal (STA) document. To clarify processes for publication of corporate press releases on UK matters a high level meeting was held in the UK between UK and corporate. In future any press release relating to UK matters originating from corporate colleagues would first be reviewed by the UK to ensure that it conformed to the Code.

The press release was reinstated unchanged by the corporate colleagues on the corporate website only after the final STA document had appeared on the NICE website in June 2007. It had since been removed from the corporate website after the submission of the present complaint to the Authority.

In response to a request for further information, Boehringer Ingelheim stated that the press release needed to be put in context since it was prepared for a global audience by German colleagues and never appeared on the UK website. UK doctors/media were never informed of or directed to the press release by Boehringer Ingelheim UK.

The content of the press release was based upon the

Final Appraisal Determination (published on the NICE website) and the Lancet publication of the SITS-MOST database. Data in the press release were given in a factual and scientific way and were direct transcripts from both these documents. The SITS-MOST was a prospective, open, multicentre, multinational, observational monitoring study for clinical centres practising thrombolysis for acute ischaemic stroke within the member states of the EU. Actilyse was licensed by the European Medicines Evaluation Agency (EMEA) in 2003 with the proviso that the SITS-MOST database was undertaken to monitor the safety and efficacy of alteplase in acute ischaemic stroke during routine clinical practice. SITS-MOST was independently run but funded by an unrestricted grant from Boehringer Ingelheim. Boehringer Ingelheim UK had no access to the SITS-MOST database or to the UK specific SITS-MOST data. The SITS-MOST database only included patients treated within the licensed indication (ie within 3 hours).

The press release stated that 'SITS-MOST recruited 6483 patients across 14 European countries and showed that mortality rates following Actilyse treatment were even lower in routine practice than had previously been seen in randomized controlled trials (11.3% v 17.3%). The incidence of symptomatic haemorrhages and functional independence at three months were comparable to those seen in randomized trials'. This was a statement of fact. In the Lancet SITS-MOST publication it was specifically stated in the findings section of the abstract '… the mortality rate at 3 months in SITS-MOST was 11.3% (701/6218: 10.5-12.1) compared with 17.3% (83/479: 14.1-21.1) in the pooled randomized clinical trials'. The reader was able to make his/her own interpretation of this statement. From a statistical point of view the confidence intervals demonstrated that the mortality data seen in the SITS-MOST database was potentially a more accurate reflection of the mortality rate that would be expected in these patients. The press release did not claim that Actilyse was a life-saving treatment.

Prior to releasing the Final Appraisal Determination NICE considered all the available evidence from the different stakeholders which included UK specific data. In Boehringer Ingelheim's view it was therefore erroneous to single out the UK-specific SITS register data over and above the other data appraised by NICE.

Additionally, with regard to the intended worldwide audience, Boehringer Ingelheim noted that under the section 'Please be advised', the press release stated that 'This release is from the corporate headquarters of Boehringer Ingelheim and is intended for all international markets. This being the case, please be aware that there may be some differences between countries regarding specific medical information including licensed uses. Please take account of this when referring to the material'. It was not intended for the UK alone.

Boehringer Ingelheim also considered that the above allegation was misleading since it did not acknowledge that the SITS-MOST data and the Final Appraisal Determination only looked at patients treated within 3 hours post stroke whereas the UK SITS data included all patients thrombolysed within and after 3 hours. Therefore the data sets were not comparable and this might account for the variations seen.

The company noted that the complainant did not refer to the point made to explain the figure of a 20.6% mortality in the UK SITS register 'Outcomes reflect the higher NIHSS (stroke severity score) of UK patients and poorer outcomes usually seen in this country but are otherwise consistent with the excellent safety profile elsewhere in Europe'. It was well known that the prognosis for patients undergoing thrombolysis for acute ischaemic stroke was much improved if the stroke was of reduced severity at onset.

PANEL RULING

The Panel noted that the press release was issued by the UK company's German corporate colleagues and placed on its corporate website. It was an established principle under the Code that UK companies were responsible for the acts/omissions of their overseas affiliates that came within the scope of the Code.

The Panel noted that the press release, dated 14 May 2007, was headed 'Actilyse (alteplase) recommended by National Institute for Health and Clinical Excellence for treatment of acute ischaemic stroke. NICE Appraisal Committee concludes that alteplase is clinically and cost effective'. Text beneath read 'For medical media, outside the US only'. The press release referred to the UK publication of the appraisal. A quotation from a senior company spokesman read '… we hope that this recommendation from NICE will allow more patients with qualifying stroke in the UK to benefit from treatment with Actilyse'. The penultimate paragraph of the 'Notes to Editor' on the final page of the press release read 'Please be advised. This release is from the Corporate Headquarters of Boehringer Ingelheim and is intended for all international markets. This being the case, please be aware that there may be some differences between countries regarding specific medical information including licensed uses. Please take account of this when referring to the material'. The Panel noted that the UK company had not referred UK doctors or media to the site. The Panel did not know whether the German company had done so. The Panel noted the comments in the press release about the intended audience. Nonetheless the Panel noted that the press release referred to a UK public document and discussed benefit to UK patients. The Panel noted that Boehringer Ingelheim twice referred to it as a press release relating to UK matters and explained that procedures had been put in place to ensure that such releases complied with the Code. The Panel considered that given its content, the press release was subject to the UK Code.

The Panel considered that the press release implied that the final NICE report had been issued and that was not so. The Panel noted that although Boehringer Ingelheim had acknowledged a breach on this point it did not consider that the complainant had made an allegation on this point and thus made no ruling on this matter.

The Panel noted that Actilyse was indicated *inter alia* for fibrinolytic treatment of acute ischaemic stroke. The summary of product characteristics (SPC) stated that such treatment must be started within 3 hours of the onset of stroke symptoms and after prior exclusion of intracranial haemorrhage by means of appropriate imaging techniques.

The Panel noted that according to the press release NICE had recommended the use of alteplase for the treatment of patients with acute ischaemic stroke. The press release referred to data in the NICE report which, based on a series of trials, demonstrated efficacy for treating acute ischaemic stroke within 3 hours and showed that 'alteplase resulted in significantly better outcomes for patients in terms of death and dependency at 3 months compared with placebo'.

The press release also explained that the NICE appraisal committee had noted the SITS-MOST data which assessed the safety and efficacy of alteplase in routine clinical practice and showed that mortality rates following alteplase treatment were 'even lower in routine clinical practice than had previously been seen in randomised clinical trials (11.3 percent vs 17.3 percent)'. More information about the SITS- MOST data appeared in the 'Notes to Editor' section.

Section 5.1 of the Actilyse SPC, Pharmacodynamic properties, Acute stroke, referred to two studies where a significantly higher proportion of patients had a good outcome (no/minimal disability) compared with placebo, results which were not confirmed in 3 other studies wherein the majority of patients were not treated within 3 hours of stroke onset. However an analysis of all patients in these studies treated within 3 hours after stroke onset confirmed the beneficial effect of alteplase. The risk difference versus placebo for a good recovery was 14.9% despite an increased risk of severe and fatal intracranial haemorrhage. The data did not allow a definite conclusion to be drawn on treatment effect on death. Nevertheless overall the benefit/risk of alteplase, given within 3 hours of stroke onset and taking into account the SPC's precautions was considered favourable.

The Panel noted that it was clear from the outset that the press release related to alteplase and treatment of acute ischaemic stroke. The Panel noted that it was acceptable to discuss the benefit which might flow from using a medicine for its licensed indication so long as such discussion was placed clearly in the context of the licensed indication and otherwise complied with the Code.

The Panel noted that the press release when discussing SITS-MOST data did not state that mortality was reduced from 17.3% to 11.3% as alleged by the complainant. Rather these figures were presented as a comparison of mortality rates seen in routine clinical practice vs randomised clinical trials. The press release made this clear. No breach of Clause 7.2 was thus ruled on this point.

The Panel noted that the press release discussed mortality data. The Panel noted the SPC statement that the data did not allow a definite conclusion to be drawn on the treatment effect on death. The press release implied that the data in this regard was unequivocal and that was not so in relation to treatment of acute ischaemic stroke. The press release was misleading in this regard and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

The Panel considered that given its rulings above high standards had not been maintained regarding the mortality data mentioned in the press release. A breach of Clause 9.1 was ruled. On balance the Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such.

Complaint received 24 July 2007

Case completed 31 October 2007