CASE AUTH/2635/8/13

ANONYMOUS v NORGINE

Promotion of Dantrolene

An anonymous, non-contactable complainant who described themself as part of the academic anaesthetic community complained about a press release for Dantrium (dantrolene) published on Norgine Pharmaceuticals UK website. Dantrium was indicated for the treatment of malignant hyperthermia (MH).

The complainant alleged that the press release headed 'New Epidemiological Study in Malignant Hyperthermia Reinforces the Effectiveness of Dantrium (Dantrolene Sodium) in Reducing Fatal Anaesthetic Reaction' was underhand promotion. It discussed an epidemiological study of survivors which did not mention mortality data in the conclusion. The complainant further alleged that the indication for dantrolene made no reference to reduction in mortality and the press release was thus not in line with the medicine's licensed indication.

The detailed response from Norgine is given below.

The Panel noted that the press release discussed Riazi *et al*. This was an epidemiological study which examined reported data on index adverse anaesthetics and evaluated associations between complications, clinical signs and dantrolene treatment to facilitate timely clinical diagnostics and treatment of MH. The Panel noted that 57 (44.2%) of patients in the study received Dantrium after an adverse anaesthetic reaction. When the time between onset of the first clinical sign and dantrolene administration was longer, the proportion of patients experiencing a complication was also larger. Data showed that for each 10 minute delay in Dantrium administration complications increased substantially; beyond 50 minutes complications increased to 100%. There were no significant differences between the group that received and the group that did not receive Dantrium as regards duration of anaesthesia, the diagnostic test for MH susceptibility, or genetic results. The study authors discussed its limitations including data availability and that the study only looked at patients who had survived the reaction and were referred for a MH susceptibility test. Overall the authors, concurring with previous studies, concluded that early diagnosis and rapid Dantrium treatment reduced MH associated complications. The study introduction noted that studies on the incidence of adverse MH reactions demonstrated a MH morbidity rate of 35% and a MH mortality rate as high as 12%.

The Panel noted that the press release began by noting the incidence of adverse anaesthetic reactions triggered by succinylcholine alone. The press release noted that Riazi *et al* supported previous findings that early recognition and prompt administration of dantrolene was critical for patient survival and reduction of complications. The press release stated that the 'study was worth noting because it also highlights how having Dantrolene readily available can reduce the morbidity and mortality caused by malignant hyperthermia and therefore suggests the importance of reviewing stock levels in hospitals'.

The Panel noted Norgine's submission that MH was often fatal if not effectively treated. Dantrium was the sole licensed treatment for the condition and its use was specified in multiple guidelines. It was recommended that it was a vital to stock dantrolene pre-emptively. The Panel also noted Norgine's submission that the epidemiology of MH and how dantrolene use might affect it at the population level was relatively less well studied and important new data rarely emerged. The Panel considered that in these circumstances, and given its comments on Riazi *et al* above, it was newsworthy. The Panel therefore did not consider that the press release had been released for promotional purposes only, as alleged. Nor did the Panel otherwise consider that the press release promoted Dantrium to the general public. No breach of the Code was ruled. The press release was not disguised promotion and no breach of the Code was ruled.

The Panel did not consider that the heading to the press release implied that Dantrium was licensed for reducing mortality as alleged. The heading 'New epidemiological study in malignant hyperthermia reinforces the effectiveness of Dantrium in reducing fatal anaesthetic reaction' clearly described the condition being treated, MH. The adjective 'fatal' was used to describe the trigger, an anaesthetic reaction. The Panel considered it would have been helpful to clearly state that the study was in survivors, and to state the licensed indication in the body of the press release rather than the editorial. The Panel noted the relationship between time of administration and complications. The Panel considered that whilst the statement in the press release that the study 'highlights how having Dantrolene readily available can reduce the morbidity and mortality caused by malignant hyperthermia and therefore suggests the importance of reviewing stock levels in hospitals' was not unreasonable in relation to morbidity it was not correct in relation to mortality as the retrospective study only examined data in survivors and this was not made clear. The claim was inaccurate and misleading in this regard. In the Panel's view, this misleading impression was compounded by two statements in the press release. The first paragraph of the press release which stated 'the study also further underlines that early recognition and prompt administration of dantrolene intravenous are critical for *patient survival* and reduction of complications' (emphasis added) and the quotation from a named doctor that 'These new data are very important

as they emphasize that survival from a malignant hyperthermia crisis, a rare condition, is highly dependent on early recognition and prompt action, and that the rapid use of dantrolene can ensure *patient survival*' (emphasis added). The Panel considered that the press release was inaccurate and therefore misleading about Riazi *et al* and mortality and breaches of the Code were ruled. The press release was not capable of substantiation in this regard; a breach of the Code was ruled. However, and on balance, the Panel did not consider that the press release implied that Dantrium was licensed to reduce mortality as alleged, nor was it inconsistent with the terms of its marketing authorisation in this regard. No breaches of the Code were ruled on this point.

The Panel considered that the company had failed to maintain high standards and a breach of the Code was ruled.

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COMPLAINT

The complainant noted that the dantrolene press release seen on Norgine's website on 16 August stated that a new study reinforced the effectiveness of dantrolene in reducing fatal anaesthetic reaction. On looking at the study abstract, the complainant noted that it was an epidemiological study of survivors and mortality data was not mentioned in the conclusion.

The study did not appear to have been conducted by Norgine but the complainant was unsure whether it had been involved in the study; it appeared on Norgine's website because it promoted dantrolene as part of a joint venture with another company. The complainant alleged that it was released for promotional purposes and as a private company it was not related to disclosure of corporate data.

Norgine appeared to the complainant to be a Dutch company but had UK media contact details. The complainant considered that the press release was underhand promotion that did not fulfil the requirements of an advertisement as described in the Code.

The complainant further alleged that the indication for dantrolene made no reference to reduction in mortality and the press release was thus not in line with the medicine's licensed indication.

When writing to Norgine, the Authority asked it to respond in relation to Clauses 3.2, 7.2, 7.4, 9.1, 12.1, 22.1 and 22.2.

RESPONSE

Norgine Pharmaceuticals Ltd passed the complaint to its parent company, Norgine BV, as the distributor for Dantrium.

Norgine submitted that it took the complaint and its commitment to adhere to the principles of the Code seriously. In order to provide context Norgine provided some background to the use of dantrolene IV. It was the sole licensed treatment for malignant hyperthermia (MH), originally licensed for that indication in 1980. MH was a rare but serious side effect of halothane anaesthesia which was widely recognised as being associated with high rates of mortality and morbidity. MH was often fatal if not effectively treated. Dantrolene sodium was currently the sole pharmacotherapeutic treatment for the condition, and its use was specified in multiple guidelines. Furthermore, guidelines listed dantrolene vials as one of the vital items to be pre-emptively stocked in all MH management kits at anaesthetic sites.

Norgine refuted that the press release breached the Code with respect to any of the clauses cited or otherwise.

Firstly, the press release was relevant to the use of dantrolene. This was supplied to journalists, as listed in the attachment provided and, in accordance with industry standard practice, posted on the media section of Norgine's corporate website. Being the only recognised and licensed treatment to be marketed for MH for over 30 years also meant that there was a large body of evidence to characterise the effects of dantrolene. However, the epidemiology of MH and how dantrolene use might affect it at the population level was relatively less well studied and important new data regarding the medicine rarely emerged. Moreover, since guidelines considered dantrolene to be an essential part of the clinical management of MH, it was inevitable that any large western-nation study into this condition would report on its use in that context.

Given the above, Norgine submitted that the Canadian study cited was from a significantly robust source and provided new relevant information. As such it was deemed newsworthy for appropriate dissemination. The corporate press release as a non-promotional factual communication was 'examined' rather than 'certified' according to the requirements of Clause 14.

Whilst maintaining that the press release was not promotional in nature, Norgine submitted that the reduction in mortality was consistent with the marketing authorisation for a product that treated an otherwise fatal outcome (in this case, MH) and was therefore in accordance with the terms of its marketing authorization and consistent with the particulars listed in its summary of product characteristics (SPC). Norgine therefore submitted that Clause 3.2 had been fully adhered to as the press release described Dantrium within the boundaries of its licence.

The press release did not make new claims regarding the effects of Dantrium, nor were there any statements regarding its efficacy or safety profile. Since Dantrium was indicated for the treatment of MH and was widely established as the de-facto treatment for MH crises it was used in subjects

in this epidemiological study. However, nothing additional regarding the product, over and above what was observed in the study, was communicated. The information communicated regarding delay to commencing infusion after diagnosis of a MH crisis was consistent with established knowledge about the condition and was communicated purely as an important finding of the study. Indeed, the headline clearly stated that the findings of the study 'reinforced' the already understood efficacy profile of dantrolene. In terms of overall content, Norgine submitted that the press release gave priority to the epidemiological and Dantrium related findings of the study.

Norgine submitted that there was a fair balance of information and that any claims/information were adequately substantiated in the press release, and reflected the totality of the relevant scientific evidence. Consequently Norgine submitted that the press release met the requirements of Clauses 7.2 and 7.4.

Norgine submitted that the press release was not a promotional item since it was a factual report of study findings. As such the intent was to direct it to appropriate journalists (a list of recipients was provided) and not to be communicated to the general public.

The press release was hosted on a media specific section of the company's corporate web site. In common with industry standard practice, new posts on the Norgine's corporate website were flagged on the homepage. Norgine provided screenshots of the website and details of how the document could be accessed.

Furthermore, Norgine submitted that given dantrolene's status as the sole treatment for MH, and the fact that it was invariably administered according to protocol in an emergency situation, there was almost no scope for a patient to request it or pressure a prescriber for it. Consequently, it was difficult to see why the marketing authorization holder or distributor would attempt to promote this product to the public as there would be no scope for pecuniary benefit.

The intent was solely to notify journalists with the intention of wider dissemination of the study findings in the medical press. Norgine submitted that the press release was fair and balanced in its content and reporting of the major study findings, as well as free from any product related efficacy or safety claims. Consequently, Norgine denied a breach of Clauses 9.1, 12.1, 22.1 or 22.2.

PANEL RULING

The Panel noted that Dantrium was indicated for the treatment of malignant hyperthermia which was a potentially fatal hypermetabolic reaction of skeletal muscle in response to administration of volatile anaesthetic drugs and/or depolarizing muscle relaxants.

Riazi *et al* was an epidemiological study which examined reported data on index adverse anaesthetics and evaluated associations between complications, clinical signs and dantrolene treatment to facilitate timely clinical diagnostics and treatment of MH. The Panel noted that 57 (44.2%) of patients in the study received Dantrium after an adverse anaesthetic reaction. The medium time between onset of the first clinical sign of such a reaction and Dantrium administration was 20 minutes with a range of 12 to 70 minutes. When the time between onset of the first clinical sign and dantrolene administration was longer, the proportion of patients experiencing a complication was also larger (23.5 vs 15 minutes, p=0.005). Data also showed that for each 10 minute delay in Dantrium administration complications increased substantially; beyond 50 minutes complications increased to 100%. There were no significant differences between the group that received and the group that did not receive Dantrium as regards duration of anaesthesia, the diagnostic test for MH susceptibility, or genetic results. The study authors discussed its limitations including data availability and the study only looked at patients who had survived the reaction and were referred for a caffeine-halothane contracture test for MH susceptibility in North America. Overall the authors, concurring with previous studies, concluded that early diagnosis and rapid Dantrium treatment reduced MH associated complications. The study introduction noted that studies on the incidence of adverse MH reactions demonstrated a MH morbidity rate of 35% and a MH mortality rate as high as 12%.

The Panel noted that the press release was headed 'New Epidemiological Study in Malignant Hyperthermia Reinforces the Effectiveness of Dantrium (dantrolene sodium) in Reducing Fatal Anaesthetic Reaction'. The press release began by noting the incidence of adverse anaesthetic reactions triggered by succinylcholine alone. It noted that Ziazi *et al* supported previous findings that early recognition and prompt administration of dantrolene was critical for patient survival and reduction of complications. Some study methodology and outcomes were outlined including the reduced incidence of complications with Dantrium and the relationship between the time of administration and complications. The press release stated that the 'study was worth noting because it also highlights how having Dantrolene readily available can reduce the morbidity and mortality caused by malignant hyperthermia and therefore suggests the importance of reviewing stock levels in hospitals'. The editorial details gave information about MH, dantrolene's licensed indication and Norgine.

The Panel noted Norgine's submission that MH was often fatal if not effectively treated. It was the sole licensed treatment for the condition and its use was specified in multiple guidelines. It was recommended that dantrolene was a vital item to be stocked pre-emptively in all MH management kits at anaesthetic sites. The Panel also noted Norgine's submission that the epidemiology of MH and how dantrolene use might affect it at the population level was relatively less well studied and important new data rarely emerged. The Panel considered that in these circumstances, and given its comments on Riazi *et al* above, the study was newsworthy. The Panel therefore did not consider that the press

release had been released for promotional purposes only, as alleged. Nor did the Panel otherwise consider that the press release promoted Dantrium to the general public. No breach of Clause 22.1 was ruled. As the press release was not promotional its nature in this regard could not be disguised, no breach of Clause 12.1 was ruled.

The Panel did not consider that the heading to the press release implied that Dantrium was licensed for reducing mortality as alleged. The heading 'New epidemiological study in malignant hyperthermia reinforces the effectiveness of Dantrium in reducing fatal anaesthetic reaction' clearly described the condition being treated, MH. The adjective 'fatal' was used to describe the trigger, an anaesthetic reaction. The Panel considered it would have been helpful to clearly state that the study was in survivors, and to state the licensed indication in the body of the press release rather than the editorial. The Panel noted the relationship demonstrated in Riazi *et al* between time of administration and complications. The Panel considered that whilst the statement in the press release that the study 'highlights how having Dantrolene readily available can reduce the morbidity and mortality caused by malignant hyperthermia and therefore suggests the importance of reviewing stock levels in hospitals' was not unreasonable in relation to morbidity it was not correct in relation to mortality as the retrospective study only examined data in survivors and this was not made clear. The claim was inaccurate and misleading in this regard. In the Panel's view, this misleading impression was compounded by two statements in the press release. The first paragraph of the press release which stated 'the study also further underlines that early recognition and prompt administration of dantrolene intravenous are critical for *patient survival* and reduction of complications' (emphasis added) and the quotation from a named doctor that 'These new data are very important as they emphasize that survival from a malignant hyperthermia crisis, a rare condition, is highly dependent on early recognition and prompt action, and that the rapid use of dantrolene can ensure *patient survival*' (emphasis added). The Panel considered that the press release was inaccurate and therefore misleading about Riazi *et al* and mortality and ruled a breach of Clauses 7.2 and 22.2. The press release was not capable of substantiation in this regard; a breach of Clause 7.4 was ruled. However, on balance, the Panel did not consider that the press release implied that Dantrium was licensed to reduce mortality as alleged, nor was it inconsistent with the terms of its marketing authorisation in this regard. No breach of Clauses 3.2 and 7.2 were ruled on this point.

Noting its rulings above the Panel considered that the company had failed to maintain high standards and ruled a breach of Clause 9.1.

Complaint received **20 August 2013**

Case completed **18 October 2013**