CASE AUTH/2183/11/08

MERZ PHARMA v ALLERGAN

Botox representative activity

Merz Pharma complained about the activities of Allergan representatives in relation to the promotion of Botox (botulinum toxin). Merz supplied Xeomin (also botulinum toxin).

Merz stated that following the Toxins Conference in Italy in June physicians reported that Allergan representatives were stating that Xeomin was only 70% as potent as Botox. This was confirmed on 1 October by a named health professional, who told a Merz representative that an Allergan representative had claimed that the dosing ratio of Xeomin to Botox was 0.7:1.

At the Toxins Conference Allergan published a poster suggesting that, based upon an Allergan test of potency on three vials of Xeomin, the potency of Xeomin was considerably less than that of Botox (Brown *et al* 2008). This animal study clearly did not agree with the two largest clinical trials conducted with Xeomin vs Botox (Jankovic 2003, Benecke *et al* 2005), other animal data presented at the meeting (Dressler 2008) or the summaries of product characteristics (SPCs) for the two products that had identical dosing regimens.

Merz knew that directly following this conference Allergan representatives had a two day training meeting. It was after this training that Merz received reports from the field about the claim of lower potency.

Merz explained that due to the toxicity of botulinum toxins, European regulators had issued a 'Dear Doctor' letter in 2007 warning health professionals about their potential systemic toxic effects and strongly advising them not to exceed the recommended dose. Clearly Allergan representatives telling health professionals that Xeomin was less potent might lead health professionals to overdose patients by up to 40% with Xeomin. Merz was very concerned that this activity could compromise patient safety.

The fact that communication of these data was part of the wider corporate communications strategy of Allergan was further reinforced with the reprinting and distribution of a poster entitled 'Substandard potency of Xeomin in the Botox mouse LD_{50} assay' at the recent European Dystonia Federation (EDF) Meeting held in Germany in October. The poster (Hunt and Clarke 2006) detailed an Allergan study and stated the potency of Xeomin at 69% of that of Botox; it was offered by representatives and was freely available from the display rack of the promotional stand at this meeting. Merz picked up several copies. In Allergan's response to Merz's concerns it stated explicitly that it had 'vigorously argued against' the use of fixed ratios citing 'regulatory approvals across Europe'. This was at odds with the activity that took place at Dystonia Europe and the multiple reports that Merz had received from customers.

Such activity by Allergan representatives was inaccurate, misleading and did not lead to the rational use of either Botox or Xeomin. As reports of this activity started following a two day briefing meeting Merz concluded that the representatives were provided with and briefed on this data, which was contrary to both SPCs. Breaches of the Code were alleged.

In Case AUTH/2117/4/08 Allergan successfully challenged Merz using direct comparison of toxin doses. Thus Allergan's current activity showed a disregard for the Authority's rulings and potentially compromised patient safety; it was a failure to maintain high standards and a promotional activity likely to bring discredit upon the industry in breach of the Code including Clause 2.

The detailed response from Allergan is given below.

The Panel examined the material provided by Allergan. It noted Merz' allegation that an Allergan representative had claimed that the dosing ratio of Xeomin to Botox was 0.7:1. At a conference in Italy Allergan had published a poster based on an Allergan test of potency of three vials of Xeomin (Brown *et al*). The poster was headed 'Xeomin displays lower potency and is neutralized by anti-Botox antibodies'. This concluded that in a mouse assay with lower potency and similar antigenicity, Xeomin was not dose-equivalent to Botox.

At a conference in Germany Allergan had distributed a poster (Hunt and Clarke) entitled 'Substandard Potency of Xeomin in the Botox Mouse LD_{50} Assay'. The poster concluded that the potencies of three lots of Xeomin were substantially lower than the labelled 100U/vial when tested in the Botox LD_{50} mouse assay and that the results confirmed that the potency of Xeomin was not equivalent to that of Botox.

Merz referred to Dressler presented at the same meeting as Brown *et al*. Dressler was headed 'Equivalent Potency of Xeomin and Botox' and concluded from 5 batches of Xeomin and Botox using the LD_{50} bioassay that the biological potencies of Xeomin and Botox were equivalent. It further stated that conversions could be performed at a 1:1 conversion ratio allowing easy exchange of both medicines in a therapeutic setting.

The Panel noted that the Botox SPC stated that botulinum toxin units were not interchangeable from one product to another. The Xeomin SPC stated due to differences in the LD_{50} assay these units were specific to Xeomin and were not interchangeable with other botulinum toxin preparations.

The Panel noted that Allergan UK stated that it did not hold any promotional activities at the two European meetings nor did it sponsor physicians to attend. There were Allergan stands at both meetings. It was not clear whether Allergan UK had held non promotional activities at the meetings. However in the Panel's view the complaint concerned the conduct of representatives in the UK and not the European meetings.

The Panel examined the materials provided by Allergan. The product monograph was dated November 2007. Page 18 compared enzymatic activity results between Botox and Xeomin. The test referred to Hunt and Clarke and their findings that 100 Xeomin units were not equivalent to 100 Botox units and that Xeomin showed substantially lower potency than the Botox reference standard. This section made it clear that the products should not be interchanged in clinical practice since it was not possible to apply a simple conversion factor and it was not recommended to attempt to fix a dose ratio. Reference was also made to the SPC statements that biological units were not applicable to any other product. The product monograph also recommended that physicians gained experience with one or more formulations and avoided changing patients between formulations wherever possible unless this was the only option for successful treatment. The product monograph concluded that there were clear differences between, *inter alia*, Botox and Xeomin in terms of potency and migration. As such there was no comparability between the different preparations and it was not possible to establish a dose ratio conversion since none of the products were interchangeable.

The Allergan competitor update presentation in May 2008 included a graph showing a light-chain activity kinetic comparison of Botox and Xeomin in which the activity of Botox appeared to be twice that of Xeomin. This was referenced to data on file. Within an SPC comparison section a slide headed 'Botox v Xeomin' included the bullet points 'Potency', 'Safety', Lack of data' and 'Licensed indications' but no further details were given.

The detail aid did not compare the products. The objection handler (dated October 2007 and according to Allergan put on hold until February 2008) included information about Xeomin. One page was headed 'Botox and Xeomin do not have equivalent potency' referenced to Hunt and Clarke. A bar chart comparing average corrected potency (Botox LD_{50} units per vial) showed Botox at 95 and Xeomin at 69, 75 and 78. Adjacent to the bar chart was the claim 'The potencies of the 3 unexpired lots of Xeomin were substantially lower than Botox when tested in the Botox mouse LD_{50} assay'.

The Panel considered that given the comparative potency information in the product monograph and the objection handler it was not unrealistic that representatives might have used this information when promoting Botox to health professionals. There was no instruction about how to use the information comparing the potency of Xeomin and Botox. The Panel considered that on the balance of probabilities Allergan's representative had claimed there was a difference in potency for the products. This was inconsistent with the SPCs which had similar dosing regimens for the products. The Panel accepted there was some animal data that possibly showed a difference. However the supplementary information to the Code was clear that animal data should not be extrapolated to the clinical situation unless there was data to show it was of direct relevance and significance. This had not been demonstrated. The Panel considered that the product monograph and the objection handler were misleading with regard to the information about potency. The comparison could not be substantiated and did not reflect all the evidence. The material would not encourage the rational use of a medicine. Thus the Panel ruled breaches of the Code. The Panel considered that as the briefing material did not comply with the Code there was also a breach in that regard. The Panel considered that high standards had not been maintained and a breach was ruled. The Panel did not consider the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

Merz Pharma UK Ltd complained about the activities of Allergan Ltd representatives in relation to the promotion of Botox (botulinum toxin). Merz supplied Xeomin (also botulinum toxin).

COMPLAINT

Merz stated that following the Toxins Conference in Baveno, Italy (12-15 June) physicians reported that Allergan representatives were stating that Xeomin was only 70% as potent as Botox. This was confirmed on 1 October by a named health professional, who told a Merz representative that an Allergan representative had claimed that the dosing ratio of Xeomin to Botox was 0.7:1.

At the Toxins Conference Allergan published a poster suggesting that, based upon an Allergan test of potency on three vials of Xeomin, the potency of Xeomin was considerably less than that of Botox (Brown *et al* 2008). This animal study clearly did not agree with the two largest clinical trials conducted with Xeomin vs Botox (Jankovic 2003, Benecke *et al* 2005), other animal data presented at the meeting (Dressler 2008) or summaries of product characteristics (SPCs) for the two products that had identical dosing regimens.

Merz knew that directly following this conference Allergan representatives had a two day training meeting. It was after this training that Merz received reports from the field about the claim of lower potency.

Botulinum toxins were the most toxic substance known to man and had been the subject of a European Medicines Agency Pharmacovigilance Working Party in 2007 that resulted in a 'Dear Doctor' letter being issued. This letter warned about the potential systemic toxic effects of toxins and strongly advised health professionals not to exceed the recommended dose. Clearly Allergan representatives telling health professionals that Xeomin was less potent might lead health professionals to overdose their patients by up to 40% with Xeomin. It was possible therefore that this activity could compromise patient safety. This gave Merz great cause for concern.

The fact that communication of these data was part of the wider corporate communications strategy of Allergan was further reinforced with the reprinting and distribution of a poster entitled 'Substandard potency of Xeomin in the Botox mouse LD_{50} assay' at the recent European Dystonia Federation (EDF) Meeting held in Hamburg, 17-19 October. The poster (Hunt and Clarke 2006) detailed and Allergan study and stated the potency of Xeomin at 69% of that of Botox; it was offered by representatives and was freely available from the display rack of the promotional stand at this meeting. Merz personnel picked up several copies. In Allergan's response to Merz's concerns it stated explicitly that it had 'vigorously argued against' the use of fixed ratios citing 'regulatory approvals across Europe'. This was at odds with the activity that took place at Dystonia Europe and the multiple reports that Merz had received from customers including verbal communications and slide presentations.

Such activity by Allergan representatives was inaccurate, misleading, and did not lead to the rational use of either Botox or Xeomin. Breaches of Clauses 7.2, 7.3 and 7.10 of the Code were alleged.

As reports of this activity started following a two day briefing meeting Merz concluded that the representatives were provided with and briefed on this data, which was contrary to both SPCs. A breach of Clause 15.9 was alleged.

In Case AUTH/2117/4/08 Allergan successfully challenged Merz using direct comparison of toxin doses. Thus Allergan's current activity showed a disregard for the Authority's rulings and potentially compromised patient safety; it was a failure to maintain high standards and a promotional activity likely to bring discredit upon the industry in breach of Clauses 9.1 and 2.

Whilst it was not possible for Merz to have access to the training or other materials issued to Allergan representatives the chronology of the activity and the specificity of the information provided by the health professional and others were convincing enough for Merz to have little doubt that this activity took place.

Merz had made every effort to resolve this dispute. Allergan had rejected Merz's request that it brief its sales force on the respective SPC guidance for both products given the potential patient safety issues.

Allergan had been informed of Merz's intention to proceed to a formal complaint.

RESPONSE

Allergan welcomed the opportunity to respond to the allegations raised by Merz and had tried to tease out the various issues raised in its letter. Some of the issues raised seemed to be new and were not the subject of the earlier correspondence.

1 Initial complaint regarding a representative and alleged briefing document to the sales force

As could be seen from the inter-company dialogue the thrust of the initial complaint from Merz related to alleged activities by a single representative and the belief that a briefing had been sent to the sales force to support or encourage the representative in these activities.

Allergan responded to the initial complaint and, when provided with the details of the representative involved, fully investigated the allegations. Allergan confirmed on 31 October that the representative had not, and was not, using any confidential Merz sales data as alleged. On a wider point, Allergan reassured Merz that it had not briefed its sales representatives to disparage Xeomin or Merz, nor had it supplied any materials to support such an activity.

Therefore, on this specific issue Allergan strongly denied the alleged breaches of Clauses 7.2, 7.3, 7.10, 15.9, 9.1 and 2.

2 Alleged patient safety issue and request to issue a briefing to the Allergan sales force

On the wider issue of patient safety, Allergan took very seriously any concerns regarding patient safety. It confirmed that its representatives did not have any materials that promoted a dosing ratio of 0.7:1 or any other fixed ratio. Indeed any use of a fixed dose ratio for any of the botulinum toxins was something Allergan had vigorously argued against with competitors for many years and would continue to clarify this position with clinicians if they were in any doubt on this issue.

Accordingly, Allergan did not believe there were any grounds to request that it issue any briefing on this matter to its sales representatives.

Allergan had not engaged in any activity which showed a disregard for the ruling of the Authority, potentially compromised patient safety or had not maintained high standards. Allergan strongly refuted the alleged breaches of Clause 9.1 or 2.

3 Toxins 2008 Conference in Baveno, Italy and alleged two day training meeting

Allergan was unclear as to why the Toxins Conference had been raised at this juncture and the relevance to this complaint. Allergan UK did not sponsor any physicians to attend the conference and nor did Allergan UK hold any promotional activities at the meeting.

A number of UK physicians would have attended as this was one of the major conferences for specialists working with botulinum toxins. Indeed, Allergan believed a number of UK physicians were sponsored by Merz to attend.

There was a full scientific programme at the meeting and 158 abstracts were presented. During the conference there was a scientific session at which each of the companies which marketed a botulinum toxin (Merz, Allergan, Ipsen and Solstice) presented scientific data on their respective products. This session produced considerable debate about the question of interchangeability and the different properties of the different botulinum toxin products. It was most likely that genuine legitimate scientific exchange at this conference had raised the comparison of the two products and interest in the range of data published on the products including the abstracts by both Brown *et al* and Dressler.

Following the Toxins Conference, Merz had alleged that 'the Allergan representatives had a two day training meeting'. Allergan confirmed that no such meeting for Allergan UK representatives took place.

4 European Dystonia Federation (EDF) Meeting 2008, Hamburg, Germany

Allergan was unclear why the EDF Meeting had been raised at this juncture and the relevance to this complaint. Allergan UK did not sponsor any physicians to attend the conference and nor did Allergan UK hold any promotional activities at the meeting.

There was a full scientific programme at the meeting. It was most likely that genuine legitimate scientific exchange at this conference, and others, had raised the comparison of the two products and interest in the range of published data including the abstract by Hunt and Clarke.

Overall, this entire complaint was based on supposition and allegation with no direct supporting evidence.

In conclusion, Allergan strongly denied the alleged breaches of Clauses 7.2, 7.3, 7.10, 15.9, 9.1 or 2.

FURTHER RESPONSE

Following a request for further information Allergan provided copies of material used by the representatives in the last six months to promote Botox. These being:

- An SPC comparison document
- Presentation slides from a competitor update session held at the UK Neurosciences Sales Meeting 14-15 May 2008. Following release of the objection handler to the sales force, training on its use was undertaken via workshops and role play. It was designed for reactive use only and was not a key part of the T2 campaign. The T2 training session campaign implementation presentation and workbook used at the meeting were also provided although there was no specific mention of Xeomin in these documents.
- At the subsequent UK Neurosciences Sales Meeting (10-12 September 2008) the focus was again on delivering the core Botox campaign – 'right muscles' and 'right dose'. The first day focussed on workshop training provided by an external expert and professor of rehabilitation medicine. The second day focussed on selling skills. There were no sessions or briefings provided on Xeomin.

The sales representatives had not been given copies of Brown *et al* or Hunt and Clarke. Data taken from Hunt and Clarke was included in the certified objection handler and in the certified product monograph.

PANEL RULING

The Panel examined the material provided by Allergan. It noted Merz' allegation that an Allergan representative had claimed that the dosing ratio of Xeomin to Botox was 0.7:1. At a conference in Italy Allergan had published a poster based on an Allergan test of potency of three vials of Xeomin (Brown *et al*). The poster was headed 'Xeomin displays lower potency and is neutralized by anti-Botox antibodies'. This concluded that in a mouse assay with lower potency and similar antigenicity, Xeomin was not dose-equivalent to Botox.

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The Panel considered that as the briefing material did not comply with the Code there was also a breach of Clause 15.9.

The Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled. The Panel did not consider the circumstances warranted a ruling of a breach of Clause 2 which was a sign of particular censure and reserved for such use.

Complaint received **13 November 2008**

Case completed **28 January 2009**