CASE AUTH/2119/4/08

ALLERGAN v MERZ PHARMA

Promotion of Xeomin

Allergan complained about the promotion of Xeomin (*clostridium botulinum* neurotoxin type A, free of complexing proteins) by Merz Pharma. The materials at issue were a BMJ advertisement, a leavepiece and stand panels used at the Association of British Neurologists (ABN) conference in Ireland in March 2008. Allergan supplied Botox (botulinum toxin (from *clostridium botulinum*) type A).

Allergan believed the claim 'Neurotoxin you need – complexing proteins you don't' in the journal advertisement made a bold statement of fact regarding the relevance of complexing proteins. It clearly implied that complexing proteins present in botulinum toxin type A products, *per se*, were not required and played no role in a product's efficacy or safety profile. While this might be true for Xeomin, this was not the case for all botulinum toxin type A products, including Allergan's product Botox.

Allergan did not accept, as submitted by Merz, that the claim made no comment concerning the role of complexing proteins. There was a comparison between Xeomin and other botulinum toxin type A products. It was disingenuous to suggest that the claim would be considered to apply only to Xeomin.

Allergan submitted that the role of complexing proteins was still one of scientific debate. The size of the botulinum toxin complex was thought likely to account for some of the clinical differences seen when comparing botulinum toxin molecules. The potential role of the accessory (complexing) proteins might confer an advantage in persistency in the target muscle versus naked neurotoxin. The issue had not been resolved in favour of one generally accepted viewpoint as indicated in the Xeomin advertisement.

Allergan alleged that the claim was not an accurate, balanced or objective evaluation of the scientific evidence.

The Panel noted that Xeomin was free from complexing proteins whilst Allergan's product, Botox, was not. The two products had been compared in a parallel group study which demonstrated non-inferiority of Xeomin (n=232) vs Botox (n=231) across various endpoints in the treatment of cervical dystonia. The authors concluded that complexing proteins were dispensable for clinical efficacy (Benecke *et al*). A similar study compared the two products in the treatment of belpharospasm. The results demonstrated the non-inferiority of Xeomin to Botox in terms of efficacy and a comparable safety profile for the two products (Roggenkämper *et al*).

The Panel noted that the role and clinical significance of the complexing proteins was one of scientific debate. The claim at issue appeared above the picture of a horse chestnut emerging from its spiky shell. The Panel considered that there was an implied comparison of Xeomin with other botulinum products. Furthermore the Panel considered that the claim at issue implied a proven clinical disadvantage for those products associated with complexing proteins for which there was no supporting data. This impression was strengthened by the picture of the chestnut (the neurotoxin) and its spiky shell (the complexing proteins). The Panel considered that the claim was misleading and a breach of the Code was ruled.

Allergan alleged that the claim 'In addition, Xeomin does not require refrigeration (prior to reconstitution) – reducing the risk of therapy failure or product wastage due to a gap in the cold chain' in the journal advertisement disparaged its product, Botox, which required refrigeration, and Allergan's cold chain supply procedures. This alleged 'risk' was based on speculation not fact. Allergan was not aware of any evidence of this 'reduced risk' with Xeomin and there was a clear implication of 'reduced risk' vs another botulinum toxin type A. All products if not stored correctly were at equal 'risk' of therapy failure or wastage.

The Panel considered that the claim at issue '… Xeomin does not require refrigeration (prior to reconstitation) – reducing the risk of therapy failure or product wastage due to a gap in the cold chain' was not unreasonable given the Xeomin Summary of Product Characteristics (SPC) which stated that the unopened vial had a shelf life of 3 years and the reconstituted solution had demonstrated chemical and physical in-use stability for 24 hours at 2 to 8oC. This was different to other unopened botulinum toxin products which required storage in a refrigerator or freezer.

The Panel did not accept that the claim disparaged either Allergan's cold chain procedures or its product Botox. The Panel considered that gaps in the cold chain might occur once a product was delivered to a customer – they might not be the fault of the supplier. The Panel noted that there was a difference between Botox and Xeomin in relation to the storage of an unopened vial which would have important practical implications for the customer. No breach of the Code was ruled.

Allergan noted that the claims 'Neurotoxin you

need – complexing proteins you don't' and 'Therapeutic efficacy is solely a characteristic of the Botulinum neurotoxin – complexing proteins have no therapeutic effect' both appeared in the leavepiece and the first board of the stand panels. The second, even more definitive claim, was in a section of the leavepiece entitled 'What is the role of complexing proteins?' This section discussed the role of complexing proteins in the context of all botulinum toxins. As outlined previously, this issue had not been resolved in favour of one generally accepted viewpoint as would seem to be clearly indicated in the leavepiece. Therefore, Allergan did not believe the claims to be an accurate, balanced or objective evaluation of the scientific evidence.

The Panel considered that the first claim had been dealt with above. The Panel considered its ruling above was relevant to the second claim 'Therapeutic efficacy is solely a characteristic of the botulinum neurotoxin – complexing proteins have no therapeutic effect'. The exact clinical role, if any, of complexing proteins had yet to be determined. Aoki *et al* stated that it was proposed that complexing proteins affected tissue distribution of botulinum toxins and although it appeared that this had yet to be proven the claim 'complexing proteins have no therapeutic effect' did not represent the current scientific and clinical debate. The Panel thus considered that the claim was misleading and a breach of the Code was ruled.

Allergan referred to a number of claims on the leavepiece and stand panels: 'Xeomin: Comparable efficacy and safety profile to [Botox] … when compared at 1:1 dosing ratio'; 'Clinical studies have demonstrated a comparable unit 1:1 dosing ratio with [Botox]'. The Xeomin SPC stated that 'Unit doses recommended for Xeomin are not interchangeable with those for other preparations of botulinum toxin'. A similar statement was included in the SPCs for all botulinum toxins. The requirement for such a statement was to ensure that physicians knew about the lack of interchangeability between botulinum toxins to minimise the risk of adverse events, ensure good clinical practice and enhance patient safety. The claims which suggested interchangeability were alleged to be misleading and not consistent with the SPC for Xeomin.

Both claims noted above appeared in the leavepiece. The Panel noted the prominent statement in the SPC that unit doses for Xeomin were not interchangeable with those for other preparations of Botulinum toxin. The Panel considered that it was misleading and inconsistent with the SPC not to make it clear that, although in the studies cited a 1:1 dosage ratio was used, unit doses were not interchangeable. The Panel ruled breaches of the Code.

Allergan Ltd complained about the promotion of Xeomin (*clostridium botulinum* neurotoxin type A, free of complexing proteins) by Merz Pharma UK Ltd.

The materials at issue were a BMJ advertisement (ref 1012a/XEO/NOV/2007/BB), a leavepiece (ref 10/10/XEO/NOV/2007/BB) and stand panels used at the Association of British Neurologists (ABN) conference in Dublin 26-28 March 2008.

Inter-company contact had failed to resolve the issues. Allergan supplied Botox (botulinum toxin (from *clostridium botulinum*) type A).

Xeomin was indicated for the symptomatic management of blepharospasm and cervical dystonia of a predominantly rotational form (spasmodic torticollis) in adults.

Merz confirmed that the materials used in Dublin came under the scope of the Code. They were provided by Merz for the 2008 ABN conference and were over-stickered to reflect the licensed status in Ireland. The leavepiece without the aforementioned modification had been employed in the UK whereas the only additional use of the exhibition panels had been at a UK launch meeting.

1 Claim 'Neurotoxin you need – complexing proteins you don't'

COMPLAINT

Allergan believed this claim in the journal advertisement made a bold statement of fact regarding the relevance of complexing proteins. It clearly implied that complexing proteins present in botulinum toxin type A products, *per se*, were not required and played no role in a product's efficacy or safety profile. While this might be true for Xeomin, this was not the case for all botulinum toxin type A products, including Allergan's product Botox.

Allergan did not accept, as submitted by Merz, that the claim made no comment concerning the role of complexing proteins in the safety and efficacy profile of any other botulinum toxin, type A product. In the advertisement at issue and throughout the Xeomin campaign, including the leavepiece and stand panels also at issue, there was comparison between Xeomin and other botulinum toxin type A products on the market. It was disingenuous to suggest that the claim would be considered to apply only to Xeomin.

Allergan submitted that the role of complexing proteins was still one of scientific debate. The size of the botulinum toxin complex was thought likely to account for some of the clinical differences seen when comparing botulinum toxin molecules. The potential role of the accessory (complexing) proteins might confer an advantage in persistency in the target muscle versus naked neurotoxin (Aoki *et al* 2006; Foster *et al* 2006 and Johnson and Bradshaw 2001). Certainly, Allergan did not believe this issue had been resolved in favour of one generally accepted viewpoint as seemed to be indicated in the Xeomin advertisement.

Allergan did not believe the claim was an accurate, balanced or objective evaluation of the scientific evidence. Therefore, it alleged that the claim 'Neurotoxin you need – complexing proteins you don't' was in breach of Clause 7.2 of the Code.

RESPONSE

Merz stated that this claim reflected the marketing authorization for Xeomin based on its proven efficacy without the presence of complexing proteins and was consistent with the product's summary of product characteristics (SPC). It was factually accurate, balanced and reflected the up-to-date information for Xeomin. It made no comment concerning the role of complexing proteins in the safety and efficacy profile of any other botulinum toxin type A product.

Allergan supported its submission that the role of complexing proteins was one of scientific debate by suggesting that the size of the botulinum toxin complex was thought likely to account for some of the clinical differences seen when comparing botulinum toxin molecules and that accessory (complexing) proteins might confer an advantage in persistency in the target muscle versus the naked neurotoxin. To support these suggestions it had drawn evidence from three articles which were reviews and opinions. Two of these articles were published in 2006 and the authors included Allergan employees (Aoki *et al* and Foster *et al*) and the third was published seven years ago (Johnson and Bradshaw).

The opinions used to substantiate the allegations were based on animal and studies that referred to Botox, Dysport, Myobloc and Neurobloc rather than Xeomin. Johnson and Bradshaw pre-dated the introduction of Xeomin and as such the opinions expressed were made without knowledge available e of Merz's complexing protein free product. Such views could not reflect the current available information.

Aoki *et al* implied that the size of the complex in different formulations might account for some of the preclinical and clinical differences. However, the evidence was again centred on studies which preceded the introduction of Xeomin.

Foster *et al* utilised comparisons between the older botulinum products which contained complexing proteins, namely Botox, Dysport and Neuroblox and failed to include Xeomin in the comparisons.

Unlike the articles cited by Allergan, Merz's claims were supported by randomised, controlled clinical trials involving over 750 patients (Benecke *et al* 2005 and Roggenkämper *et al* 2006). Whilst the authors included Merz personnel they were based on non-refutable endpoints. Furthermore, the evidence for Xeomin had been accepted by the regulatory authorities and was included in the product's European Public Assessment Report (EPAR).

Benecke *et al* compared [Xeomin] with Botox in cervical dystonia in over 460 patients and concluded that '… noninferiority of [Xeomin] vs Botox across various endpoints. We thus conclude that the complexing proteins contained in currently marketed [botulinum type A] preparations are dispensible for clinical efficacy. The safety and tolerability profiles for both treatments were similar…'.

Such statements were clearly consistent with the concept that Xeomin demonstrated the efficacy required without the presence or need for complexing proteins.

Merz robustly contested the allegation that 'Neurotoxin you need – complexing proteins you don't' was in breach of Clause 7.2. It was based on randomised controlled clinical evidence for Xeomin which had been accepted by regulatory authorities and was consistent with the SPC. Furthermore, the evidence supplied by Allergan to support the allegation of a breach of Clause 7.2 was based on opinion centred on older studies and failed to consider the information available for Xeomin and therefore could not be considered an up-to-date evaluation of evidence.

PANEL RULING

The Panel noted that Xeomin was free from complexing proteins whilst Allergan's product, Botox, was not. The two products had been compared in a parallel group study which demonstrated non-inferiority of Xeomin (n=232) vs Botox (n=231) across various endpoints in the treatment of cervical dystonia. The authors concluded that complexing proteins were dispensable for clinical efficacy (Benecke *et al*). A similar study compared the two products in the treatment of belpharospasm. The results demonstrated the non-inferiority of Xeomin to Botox in terms of efficacy and a comparable safety profile for the two products (Roggenkämper *et al*).

The Panel noted that the role and clinical significance of the complexing proteins was one of scientific debate. The supplementary information to Clause 7.2 in relation to emerging clinical or scientific opinion stated that where a clinical or scientific issue existed which had not been resolved in favour of one generally accepted viewpoint particular care must be taken to ensure that it was treated in a balanced manner in promotional material.

The claim at issue 'Neurotoxin you need – complexing proteins you don't' appeared above the picture of a horse chestnut emerging from its spiky shell. The Panel considered that there was an implied comparison of Xeomin with other botulinum products. Furthermore the Panel considered that the claim at issue 'Neurotoxin you need – complexing proteins you don't' implied a proven clinical disadvantage for those products

associated with complexing proteins for which there was no supporting data. This impression was strengthened by the picture of the chestnut (the neurotoxin) and its spiky shell (the complexing proteins). The Panel considered that the claim was misleading and a breach of Clause 7.2 was ruled.

2 Claim 'In addition, Xeomin does not require refrigeration (prior to reconstitution) – reducing the risk of therapy failure or product wastage due to a gap in the cold chain'

COMPLAINT

Allergan alleged that this claim in the journal advertisement disparaged its product, Botox, which required refrigeration, and Allergan's cold chain supply procedures. This alleged 'risk' was based on speculation not fact.

This claim would clearly be considered by the reader within the context of the advertisement and the wider Xeomin campaign, where Xeomin was compared with other botulinum toxin type A products.

Allergan agreed that if medicines were not stored according to their licensed recommendations then there was a risk of loss of efficacy and associated wastage due to stability issues. However, the claim clearly stated 'reducing the risk' of therapy failure or product wastage due to a gap in the cold chain. Allergan was not aware of any evidence of this 'reduced risk' with Xeomin and there was a clear implication of 'reduced risk' vs another botulinum toxin type A. All products if not stored correctly were at equal 'risk' of therapy failure or wastage.

Allergan alleged a breach of Clause 8.1.

RESPONSE

Merz stated that the claim that Xeomin (prior to reconstitution) did not require refrigeration was factually accurate. Botox required refrigeration.

If any medicine was not stored according to licensed recommendations then there was a risk of loss of efficacy and associated wastage due to stability issues or even a safety risk. If there was not a risk of therapy failure or product wastage from the product not being refrigerated the regulatory authorities would not have required that this be included on the SPC.

Merz contested that it disparaged Botox in breach of Clause 8.1 as the claim was factually accurate for Xeomin and no other product was mentioned. In addition, should one choose to compare this factual property of Xeomin with Botox then it would still be fair and balanced.

PANEL RULING

The Panel considered that the claim at issue '… Xeomin does not require refrigeration (prior to reconstitution) – reducing the risk of therapy failure or product wastage due to a gap in the cold chain' was not unreasonable given the Xeomin SPC. Section 6.3 stated that the unopened vial had a shelf life of 3 years and the reconstituted solution had demonstrated chemical and physical in-use stability for 24 hours at 2 to 8°C. From a microbiological point of view the product should be used immediately. Section 6.4 stated that the unopened vial should not be stored above 25°C. This was different to other unopened botulinum toxin products which required storage in a refrigerator or freezer.

The Panel did not accept that the claim disparaged either Allergan's cold chain procedures or its product Botox. The Panel considered that gaps in the cold chain might occur once a product was delivered to a customer – they might not be the fault of the supplier. The Panel noted that there was a difference between Botox and Xeomin in relation to the storage of an unopened vial which would have important practical implications for the customer. The Panel considered the claim was not disparaging as alleged and no breach of Clause 8.1 was ruled.

3 Claims 'Neurotoxin you need – complexing proteins you don't' and 'Therapeutic efficacy is solely a characteristic of the Botulinum neurotoxin – complexing proteins have no therapeutic effect'

COMPLAINT

Allergan stated that both claims appeared in the leavepiece and the first board of the stand panels. The second, even more definitive claim, was in a section of the leavepiece entitled 'What is the role of complexing proteins?' This section discussed the role of complexing proteins in the context of all botulinum toxins and not just Xeomin, as Merz stated in inter-company dialogue. As outlined previously, with respect to the BMJ advertisement in point 1 above, Allergan did not believe this issue had been resolved in favour of one generally accepted viewpoint as would seem to be clearly indicated in the leavepiece.

Therefore, Allergan did not believe the claims to be an accurate, balanced or objective evaluation of the scientific evidence on this matter and alleged a breach of Clause 7.2.

RESPONSE

Merz submitted that its response regarding the claim 'Neurotoxin you need – complexing proteins you don't' had been addressed in point 1 above.

The claim 'Therapeutic efficacy is solely a characteristic of the Botulinum neurotoxin – complexing proteins have no therapeutic effect' was supported by clinical studies involving Xeomin which was free from complexing proteins and commercially available toxin which contained complexing proteins. The results demonstrated that Xeomin was non-inferior in terms of efficacy with no difference in side effects compared with Botox, a fact acknowledged by the article supplied by Allergan (Aoki *et al*).

Merz did not believe that the claim was in breach of Clause 7.2 as it reflected the current evidence from clinical trials and was not based on inappropriate comparisons between toxins containing complexing proteins, animal studies or opinions based on evidence which did not consider all the currently available information for Xeomin.

PANEL RULING

The Panel considered that the first claim had been dealt with in point 1 above. The second claim appeared in the leavepiece. Merz had provided one page showing the stand panel and the second claim did not appear on that.

The Panel considered its ruling in point 1 was relevant to the claim 'Therapeutic efficacy is solely a characteristic of the botulinum neurotoxin – complexing proteins have no therapeutic effect'. The exact clinical role, if any, of complexing proteins had yet to be determined. Aoki *et al* stated that it was proposed that complexing proteins affected tissue distribution of botulinum toxins and although it appeared that this had yet to be proven the claim 'complexing proteins have no therapeutic effect' did not represent the current scientific and clinical debate. The Panel thus considered that the claim was misleading and a breach of Clause 7.2 was ruled.

4 Interchangeability between botulinum toxins

COMPLAINT

Allergan referred to a number of claims on the leavepiece and stand panels:

'Xeomin: Comparable efficacy and safety profile to [Botox] in spasmodic torticollis and blepharospasm when compared at 1:1 dosing ratio'

'Clinical studies have demonstrated a comparable unit 1:1 dosing ratio with [Botox]'

In Section 4.2 of the Xeomin SPC (Posology and method of administration) it was stated that 'Unit doses recommended for Xeomin are not interchangeable with those for other preparations of botulinum toxin'. A similar statement was included in the SPCs for all botulinum toxins. The requirement by the regulatory authorities for such a statement was to ensure that physicians knew about the lack of interchangeability between botulinum toxins to minimise the risk of adverse events, ensure good clinical practice and enhance patient safety.

The claims at issue, without appropriate reference to a lack of interchangeability, were of concern and raised potential safety issues.

The claims which suggested interchangeability were alleged to be misleading and not consistent with the SPC for Xeomin, in breach of Clauses 3.2 and 7.2 of the Code.

RESPONSE

Merz stated that the claims in question were clearly referenced to the cited clinical studies (Benecke *et al* and Roggenkämper *et al*) and as might be expected referred to the dosing ratios used. This was to ensure that prescribers knew that the dosages of Botox and Xeomin employed were the same. No statement suggesting interchangeability was made.

Whilst this was the case, the EPAR (page 6) expressed the opinion that '… the data from the non-clinical and clinical development program… provided sufficient evidence that a 1:1 dose ratio between Xeomin and Botox with respect to efficacy and safety can be concluded…'.

As the statements were factually accurate and framed in the context of the cited clinical trials, balanced by additional statements with no suggestion of interchangeability, Merz contested the claim that the data presented was inconsistent with the SPC and that the information presented from the cited clinical studies was factually inaccurate. Merz denied breaches of Clauses 7.2 or 3.2.

PANEL RULING

The Panel noted that the stand panel provided by Merz made no mention of the 1:1 dosing ratio comparison. Both claims noted above appeared in the leavepiece.

The Panel noted the prominent statement in the SPC that unit doses for Xeomin were not interchangeable with those for other preparations of Botulinum toxin. The Panel considered that it was misleading and inconsistent with the SPC not to make it clear that, although in the studies cited a 1:1 dosage ratio was used, unit doses were not interchangeable. The Panel ruled a breach of Clauses 3.2 and 7.2 of the Code.

Complaint received **30 April 2008**

Case completed **2 July 2008**