CASE AUTH/2226/4/09

MERZ PHARMA v ALLERGAN

Botox product monograph

Merz Pharma alleged that a Botox (botulinum neurotoxin) monograph issued by Allergan, contained unfounded comparisons of Botox with Dysport (Ipsen's product – botulinum toxin Type A – haemaglutinin complex) that would disadvantage its product Xeomin (botulinum neurotoxin).

With regard to the claim 'In summary, the different botulinum formulations differ markedly, this can have a significant impact on clinical performance; Merz knew of no data to support the claim. Allergan had stated that it would not use this claim in future comparisons with Xeomin; however Allergan refused to substantiate the claim against Dysport. Merz alleged that the claim was not an accurate reflection of the clinical evidence and could not be substantiated.

The detailed response from Allergan is given below.

The Panel noted that there were some differences between Botox and Dysport but did not consider that these differences were so marked that they had a significant impact on clinical performance. The implied comparison was misleading and had not been substantiated as alleged. Breaches of the Code were ruled.

With regard to the claim 'Due to differences in the safety profiles, dosing should be based on individual analysis of the safety profile and efficacy of each product for each particular indication' Merz stated there was no evidence that the safety profiles differed between Botox, Xeomin and Dysport. Allergan had again refused to respond to Merz's challenge on this point.

The Panel noted that there were differences in the adverse event profiles. Chapman *et al*, a literature review noted that dysphasia was the primary treatment-related adverse event observed with botulinum toxin type A therapy for cervical dystonia and noted that caution might be warranted with the use of *inter alia*, Dysport at the higher dose range. The Dysport summary of product characteristics (SPC) listed dysphagia as a common (>1/100) adverse event when the patient was treated for arm spasticity and very common (>1/10) in the treatment of spasmodic torticollis. The Botox SPC stated that patients with cervical dystonia should be informed of the possibility of experiencing dysphagia which might be mild but could be severe and listed dysphagia as a very common adverse event in the treatment of blepharospasm or hemifacial spasm. The Panel noted that there were some differences between the safety profiles of Botox and Dysport and thus did not consider that the claim at issue was misleading or incapable of substantiation as alleged. No breaches of the Code were ruled.

Merz alleged that the claim: Botulinum toxins 'act very differently' was not a reflection of the true picture with no clinical evidence that Botox, Xeomin or Dysport acted any differently. The contrary was true with all three being type A toxins. The use of 'very' gave weight to the unsubstantiated and misleading claim.

The Panel considered that its ruling in the first point was relevant here. The Panel noted that there were differences between the products however the claim at issue '… although they are all type A serotypes, they act very differently due to differences in complex size and structure as a consequence of the purification processes' implied fundamental differences in the way the three botulinum neurotoxins acted. The Panel did not consider that any data had been presented in that regard. The claim was misleading and had not been substantiated as alleged. Breaches of the Code were ruled.

Merz did not know of any evidence that supported the claim that 'There are clear differences between these products in terms of potency and migration' for Dysport compared with Botox. Indeed, the SPCs insisted that direct comparisons of potency were not made. Merz, therefore alleged that the claim was misleading and incapable of substantiation.

The Panel noted Allergan's submission that the claim at issue summarized discussions in previous sections. The Panel noted that there were some differences between the products. Section 4.8 of the Botox SPC, Undesirable effects, noted that side effects related to spread of toxin distant from the site of administration had been reported very rarely; exaggerated muscle weakness, dysphagia, aspiration, aspiration pneumonia, with fatal outcome in some cases. A similar reference appeared in the Dysport SPC which referred to fatal outcome in some very rare cases. The Panel noted that Aoki *et al* referred to the lower molecular mass of the Dysport formulation such that it would migrate further from the injection site as a result of fluid based distribution and subsequently reach adjacent tissue or the systemic system.

The Panel noted that the Botox SPC stated that botulinum toxin units were not interchangeable from one product to another. A similar statement appeared in the Dysport SPC. The Panel noted as submitted by Allergan that there were differing opinions about the relative potencies of Dysport and Botox ranging from 1.2 to 1.11.

The Panel considered that there were some differences in relation to both migration and potency but queried whether these could be described as 'clear'. On balance the Panel ruled breaches of the Code.

Merz was particularly concerned that Allergan had refused to provide substantiation for these claims at the request of its medical director.

No data had been provided to Merz and a breach of the Code was ruled.

Merz Pharma complained about a Botox (botulinum neurotoxin) monograph (ref ACA/0343/2007) issued by Allergan. Inter-company correspondence had failed to resolve the matter. Merz supplied Xeomin (botulinum neurotoxin). Merz considered that unfounded comparisons of Botox with Dysport (Ipsen's product – botulinum toxin Type A – haemaglutinin complex) would put the promotion of Xeomin at a disadvantage.

1 Claim: 'In summary, the different botulinum formulations differ markedly, this can have a significant impact on clinical performance'

This claim appeared on page 18 of the product monograph.

COMPLAINT

Merz knew of no data that showed that any variation between Dysport and Botox had any impact upon clinical performance. Allergan had stated in previous correspondence that it would not use this claim in future comparisons with Xeomin; however Allergan refused to substantiate the claim against Dysport. Merz alleged that the claim was not an accurate reflection of the clinical evidence and could not be substantiated in breach of Clauses 7.2 and 7.4 of the Code.

RESPONSE

Allergan stated that the sentence, which immediately followed the claim at issue, 'Due to differences in the safety profiles, dosing should be based on individual analysis of the safety profile and efficacy of each product for each particular indication; gave more context.

Allergan denied a breach of Clause 7.2 or 7.4.

This claim was contained within a section entitled 'Non-Interchangeability'. The fundamental message of this section was that botulinum toxin units were not interchangeable from one product to another, as stated in the summary of product characteristics (SPCs) for Botox, Dysport and Xeomin.

A significant part of this section compared Botox with Dysport.

Regarding Xeomin, context with respect to efficacy and safety was provided with reference to the Merz non-inferiority studies (Benecke *et al* 2005, Roggenkamper *et al* 2006).

Across all three botulinum toxin type A products there were clear differences between the formulations, each preparation was manufactured using unique methods of purification and formulation (Aoki *et al*, 2006). A number of clinical studies had demonstrated differences in the comparative safety profiles of Botox and Dysport. A study investigating Botox and Dysport in the treatment of blepharospasm found a difference in adverse event rates (Nussgens and Roggenkamper, 1997). Ranoux *et al* (2002) compared Botox and Dysport in the treatment of cervical dystonia and found differences in the incidence of treatment-related adverse events between the two products. Chapman *et al* (2007) systematically reviewed and analysed published literature, focusing on cervical dystonia, to compare rates of dysphagia and dry mouth in studies of different botulinum toxin products. The authors concluded that their results indicated differences in adverse event rates between botulinum toxin preparations, suggesting that use of these products should be based on their individual dosing, efficacy and safety profiles. This systematic review also included Myobloc, a botulinum toxin type B.

As confirmed by Aoki *et al*, differences were apparent when considering the clinical application and adverse event profile of the different toxin formulations.

When considering all three botulinum toxin type A products, the doses and injection patterns varied, as well as the range of licensed indications. All this needed to be borne in mind by the clinician treating an individual patient.

PANEL RULING

The Panel noted Allergan's submission about the studies which compared, *inter alia* the safety profiles of Botox and Dysport. The Panel noted that there were some differences between the products but did not consider that these differences were so marked that they had a significant impact on clinical performance. The Panel considered the implied comparison with Dysport was misleading and had not been substantiated as alleged. A breach of Clauses 7.2 and 7.4 was ruled.

2 Claim: 'Due to differences in the safety profiles, dosing should be based on individual analysis of the safety profile and efficacy of each product for each particular indication'

This claim immediately followed the claim at issue at point 1.

COMPLAINT

Merz noted that this claim for a difference in the safety profiles of the products was unreferenced. There was no evidence that the safety profiles differed between Botox, Xeomin and Dysport. Allergan had again refused to respond to Merz's challenge on this point. Merz alleged a breach of Clauses 7.2 and 7.4.

RESPONSE

Allergan stated that in the monograph the claim regarding differing safety profiles related to the entire section on non-interchangeability discussing Botox, Dysport and Xeomin. Across the botulinum toxin type A products on the market this would seem a prudent measure for a clinician to take, in line with the SPCs for the products.

Whilst acknowledging the two non-inferiority studies (Benecke *et al*, Roggenkamper *et al*), there were differences in the safety profiles of botulinum toxin products on the market as outlined in the section above and as stated in the SPCs for Botox, Dysport and Xeomin.

As confirmed by Aoki *et al* (2006), differences were apparent when considering the clinical application and adverse event profile of the different toxin formulations.

When considering all three botulinum toxin type A products, the doses and injection patterns varied, as well as the range of licensed indications. All this needed to be borne in mind by the clinician treating an individual patient.

Allergan denied a breach of Clauses 7.2 or 7.4.

PANEL RULING

The Panel noted that there were differences in the adverse event profiles. Chapman *et al*, a literature review noted that dysphasia was the primary treatment-related adverse event observed with botulinum toxin type A therapy for cervical dystonia and noted that caution might be warranted with the use of *inter alia*, Dysport at the higher dose range. The Dysport SPC listed dysphagia as a common (>1/100) adverse event when the patient was treated for arm spasticity and very common (>1/10) in the treatment of spasmodic torticollis. Section 4.4 of the Botox SPC stated that patients with cervical dystonia should be informed of the possibility of experiencing dysphagia which might be mild but could be severe and listed dysphagia as a very common adverse event in the treatment of blepharospasm or hemifacial spasm. The Panel noted that there were some differences between the safety profiles of Botox and Dysport and thus did not consider that the claim at issue was misleading or incapable of substantiation as alleged. No breach of Clauses 7.2 and 7.4 was ruled.

3 Claim: Botulinum toxins 'act very differently'

This claim appeared on page 22 of the monograph.

COMPLAINT

Merz submitted that again this was not a reflection of the true picture with no clinical evidence that Botox, Xeomin or Dysport acted any differently. The contrary was true with all three being type A toxins. The use of 'very' gave weight to the unsubstantiated and misleading claim. The fact that it appeared in the conclusion of a much larger document was not only irrelevant (as all sections must be capable of standing alone) but compounded the problem as readers might only read the conclusion section of a large document. Whilst Allergan had agreed in previous correspondence to withdraw the claim in comparison with Xeomin it refused to withdraw the claim in comparison with Dysport. Merz alleged breaches of Clauses 7.2 and 7.4.

RESPONSE

Allergan stated that the words at issue, 'act very differently' were part of a larger paragraph on page 22 of the monograph:

> 'There are currently three available preparations of botulinum toxin type A (Botox, Dysport and Xeomin (which was recently made available in some countries in Europe) and although they are all type-A serotypes, they act very differently due to differences in complex size and structure as a consequence of the purification processes. There are clear differences between these products in terms of potency and migration. As such, there is no comparability between the different preparations and it is not possible to establish a dose ratio conversion since none of the products are interchangeable.'

The context surrounding these words had been missed. This claim was contained in the conclusion of the monograph, summarised the discussions in the previous sections, and related to the three botulinum toxin type A products on the market.

If, as suggested by Merz, readers only read the conclusion of this document there was sufficient information in the sentences immediately following the one at issue, to support the claim. The paragraph concluded that it was not possible to establish a dose ratio conversion for the products, and that the products were not interchangeable as stated in the SPCs for Botox, Dysport and Xeomin.

Allergan did not accept the assertion by Merz that the fact the words at issue were part of the conclusion of a larger document was 'irrelevant'. Here context was important, both in the

surrounding sentences and also the earlier sections, as discussed above.

Allergan denied a breach of Clauses 7.2 or 7.4.

PANEL RULING

The Panel considered that its ruling at point 1 was relevant here. The Panel noted that there were differences between the products however the claim at issue '… although they are all type A serotypes, they act very differently due to differences in complex size and structure as a consequence of the purification processes.' implied fundamental differences in the way the three botulinum neurotoxins acted. The Panel did not consider that any data had been presented in that regard. The claim was misleading and had not been substantiated as alleged. A breach of Clauses 7.2 and 7.4 was ruled.

4 Claim: 'There are clear differences between these products in terms of potency and migration'

This claim immediately followed the one at issue at point 3.

COMPLAINT

Merz stated that it did not know of any evidence that supported the claim that there were differences in potency and/or migration for Dysport compared with Botox. Indeed, the SPCs insisted that direct comparisons of potency were not made. Allergan had refused to engage in any dialogue on this point or attempted to justify it. Merz, therefore alleged, without any evidence to the contrary from Allergan, that the claim was misleading and incapable of substantiation in breach of Clauses 7.2 and 7.4.

RESPONSE

Allergan stated that the claim at issue 'There are clear differences between the products in terms of potency and migration' was part of the following paragraph:

> 'There are currently three available preparations of botulinum toxin type A (BOTOX®, Dysport and Xeomin (which was recently made available in some countries in Europe) and although they are all type-A serotypes, they act very differently due to differences in complex size and structure as a consequence of the purification processes. There are clear differences between these products in terms of potency and migration. As such, there is no comparability between the different preparations and it is not possible to establish a dose ratio conversion since none of the products are interchangeable.'

The context surrounding this claim had been missed. This claim was contained in the conclusion of the monograph, summarised the discussions in the previous sections, and related to the three botulinum toxin type A products on the market.

As discussed in the section on non-interchangeability (page 17 of the monograph) there were differing opinions as to the relative potencies of Botox and Dysport. These had ranged from 1:2 to 1:11 (Marchetti *et al*, 2005). The published data therefore supported the assertion that a fixed dose ratio could not be used when comparing the two toxins and that there was a range of ratios dependent on patient populations and indications. Regarding botulinum toxin diffusion/migration, full dose-response curves could not be generated with botulinum toxins in humans for obvious ethical reasons and thus preclinical models were useful in this regard. Differences in safety margins seen in animal models might result from differences in formulation and molecular size (Aoki *et al*). The claim at issue did not suggest that this matter had been resolved in favour of one generally accepted viewpoint. It merely summarised the presented data and the fact that between all three botulinum toxin type A products there were differences.

Allergan could not agree to Merz's broad request not to make any claims suggesting differences in potency and/or migration between any of the botulinum toxin type A products on the market. This very broad request, seemed inappropriate, and Allergan believed should not be part of the complaint process. Again, the suitability of such a claim would depend on the context and the supporting evidence provided.

Allegan denied breaches of Clauses 7.2 or 7.4.

PANEL RULING

The Panel noted Allergan's submission that the claim at issue summarized discussions in previous sections. The Panel noted that there were some differences between the products. Section 4.8 of the Botox SPC, Undesirable effects, noted that side effects related to spread of toxin distant from the site of administration had been reported very rarely; exaggerated muscle weakness, dysphagia, aspiration, aspiration pneumonia, with fatal outcome in some cases. A similar reference appeared in the Dysport SPC which referred to fatal outcome in some very rare cases. The Panel noted that Aoki *et al* referred to the lower molecular mass of the Dysport formulation such that it would migrate further from the injection site as a result of fluid based distribution and subsequently reach adjacent tissue or the systemic system.

The Panel noted that the Botox SPC stated that botulinum toxin units were not interchangeable from one product to another. A similar statement appeared at Section 4.2 of the Dysport SPC. The

Panel noted as submitted by Allergan that there were differing opinions about the relative potencies of Dysport and Botox ranging from 1.2 to 1.11.

The Panel considered that there were some differences in relation to both migration and potency but queried whether these could be described as 'clear'. On balance the Panel ruled a breach of Clauses 7.2 and 7.4 of the Code.

5 Request for information

COMPLAINT

Merz was particularly concerned that Allergan had refused to engage with it and provide it with data concerning these claims. If Allergan subsequently provided data to the Panel that it refused to provide to Merz this would clearly be a deliberate ploy to put Merz at a disadvantage in front of the Panel. Merz alleged a breach of Clause 7.5 of the Code as Allergan had refused to provide substantiation for these claims at the request of the Merz medical director (a member of the health professions).

RESPONSE

Allergan did not believe that complaints about possible theoretical future use of claims could be considered by the Authority. Hence Allergan's response to Merz regarding the open-ended nature of its request.

Allergan had entered into extensive and protracted correspondence and two Code cases around claims, taken out of context, from a withdrawn item.

Merz appeared to be anticipating the way Allergan might use potential claims in the future – which Allergan did not believe was the role of the complaints process.

PANEL RULING

The Panel noted Merz's letter dated 2 April wherein it requested substantiation for certain claims. The Panel did not consider, as stated by Allergan, that this was a speculative request requiring Allergan to justify how it might use such claims in the future. The request related, *inter alia*, to comparative claims in the product monograph in relation to Dysport and Botox. No data had been provided to Merz. A breach of Clause 7.5 was ruled.

Complaint received **23 April 2009**

Case completed **26 June 2009**