CASE AUTH/2778/8/15

MERZ v IPSEN

Promotion of Dysport

Merz complained about two leavepieces for Dysport (a botulinum toxin type A (BoNT-A) product) issued by Ipsen. The leavepieces detailed dose ratios for Dysport vs other BoNT-A medicines (including Merz's product Xeomin); one leavepiece was based on dosing data from summaries of product characteristics (SPCs), and the other on a systematic review of published clinical studies.

Merz was concerned that Ipsen appeared to wish to claim that there was an unpredictable dose-response relationship (dose ratio) between the different BoNT-A medicines on the market. Ipsen explained that the two leavepieces were part of a campaign to dispel the myth that a blanket, single dose ratio could be applied across all indications. The detailed response from Ipsen is given below.

With regard to the leavepiece based on data from the SPCs, Merz stated that regulatory studies often used different endpoints and so data derived from them was not suitable for an indirect comparison. Further, to indirectly derive dose ratios from SPC data was unacceptable and misleading.

The Panel considered that the leavepiece at issue clearly compared the dosage information taken from the SPCs for Dysport, Botox and Xeomin. Although SPC doses were derived from registration studies, the Panel did not consider that the leavepiece was a comparison of these studies *per se* as alleged. In that regard no breach of the Code was ruled. The Panel noted that the aim of the leavepiece was to counter a claim that a single dose ratio could be applied across the board when changing patients from Dysport to another BoNT-A. In terms of recommended initial doses of shared indications for Dysport and Xeomin only one dose ratio was stated ie 1.6:1 for the treatment of blepharospasm. In terms of maximum doses for the two medicines dose ratios of 3.3:1 and 2.4:1 were given for cervical dystonia and for blepharospasm respectively. This countered a single blanket dose ratio switch. Nonetheless, in the Panel's view, the leavepiece appeared to give unequivocal, recommended Dysport:other BoNT-A dose ratios for each indication listed. In the Panel's view this was misleading as each dose ratio given was based on an indirect comparison of SPC doses for Dysport and the other medicine, not on a head-to-head clinical study of the two; the claims could not be substantiated. Breaches of the Code were ruled.

Merz further alleged that the dose ratios based on the maximum doses of the BoNT-A medicines ignored potential consequences of switching and did not encourage the rational use of medicines. Merz noted a dose ratio of 3.3:1 (Dysport: Xeomin) had been presented for cervical dystonia. This meant that if a patient was receiving 750-1000 units of Dysport (recommended range 250-1000 units; the SPC stated that higher doses were associated with an increase in side-effects), they would require 227-300 units of Xeomin – well about the normal recommended maximum dose of 200 units (although the SPC stated that up to 300 units might be given).

The Panel noted that the leavepiece stated, without explanation, that the recommended maximum dose of Xeomin for cervical dsytonia was 300 units. The maximum recommended dose for Dysport in the treatment of cervical dystonia was simply stated to be 1000 units and the resultant dose ratio for Dysport:Xeomin at the maximum dose of each was stated to be 3.3:1. Overall the Panel considered that the references to the maximum doses of Dysport and Xeomin in the leavepiece did not accurately reflect the information given in the SPC or alert the reader that more details, particularly about side effects, should be sought. In that regard, and contrary to Ipsen's submission, the Panel did not consider that the statement at the top of the table that the products' SPCs should be consulted for full prescribing information was sufficient. In the Panel's view, the simplistic way in which the information had been presented did not encourage the rational use of the medicines. A breach of the Code was ruled.

Merz noted that the leavepiece based on data from a systematic review of published studies was incomplete in that at least two studies which involved Dysport and Xeomin had not been included.

The Panel noted that the leavepiece (dated January 2014) detailed a meta-analysis conducted in February 2012; it had not been updated to reflect a subsequent meta-analysis conducted in September 2014 and nor did it include data on Dysport:Xeomin which had since been published. The front page of the leavepiece clearly stated that 'no studies compared Dysport and Xeomin'. In so much as it did not detail the 2014 meta-analysis (even assuming that the recently published Dysport: Xeomin studies did not meet the eligibility criteria) the Panel considered that the leavepiece was not based on an up-to-date evaluation of all the data. In the Panel's view, readers would assume that all of the relevant data had been included which was not so. Breaches of the Code were ruled.

Merz alleged that if the two leavepieces were used together, questions posed in the one based on clinical data eg 'Does a single dose ratio exist?' would appear to be answered by the comparison of the SPC doses in the other. Further breaches of the Code were alleged.

The Panel considered that the two leavepieces were inextricably linked and that its rulings above about the leavepiece based on SPC data applied to their combined use.

Merz Pharma UK Limited complained about the promotion of Dysport (a botulinum toxin type A (BoNT-A) product) by Ipsen Limited. The materials at issue were two leavepieces which detailed dose ratios for Dysport compared with other BoNT-A medicines (Allergan's Botox and Merz's Xeomin). The first leavepiece (ref UK/DYS08687(1)), based on data from summaries of product characteristics (SPCs), was headed 'Comparison of SPC Doses' and subheaded 'Ratios derived from SPC doses highlight the variation across indications'. The second leavepiece (ref UK/DYS08686(1)) was entitled 'Botulinum Toxins – The Ratio Challenge' and referred to a systematic review conducted by a life sciences consultancy in February 2012 which calculated dose ratios based on relevant published clinical studies.

Background to the complaint

Merz explained that following feedback from the field and a teleconference with Ipsen it appeared that Ipsen wished to claim that there was a non-linear, or in some way unpredictable, dose-response relationship (dose ratio) between the different BoNT-A products on the market. The consequence of this proposition was that it would not be possible to satisfactorily change patients from one BoNT-A product to another. Merz believed that this position was derived from a commercial defence strategy to slow erosion of Ipsen's market share in the BoNT-A therapeutic market.

To develop this argument Ipsen had manufactured a table of dose ratios from the extrapolation of data which was fundamentally not suitable for comparison. Further, it had failed to balance these data through the deliberate exclusion of recently published, appropriate, well designed comparative and switch studies which contradicted this story. Merz thus considered that the leavepieces provided an incomplete analysis of the data, and a deliberate failure to represent publications which conflicted with Ipsen's message. Merz was concerned that these actions were fundamentally misleading, did not encourage the rational use of medicines and were not in the interests of patient safety.

By way of background, and with regard to the context of the two leavepieces in question, Ipsen submitted that it produced three leavepieces, 'Comparison of SPC Doses' (Point 1 below), 'Botulinium toxins – The Ratio Challenge' (Point 2 below) and 'Considerations for Pharmacists' (not at issue in this complaint) which together constituted the 'Dispelling the Myth' campaign launched in April 2013. The objective of the three leavepieces was to dispel the myth that a single dose ratio could be replicated across all the indications and across an entire health economy with different injectors. Ipsen recognised the challenges health economies faced in managing services and budgets; they were being presented with tender propositions recommending a blanket switch from Dysport at a 4:1 dose ratio which proposed significant cost savings to medicine budgets. Ipsen was anecdotally aware that where clinics or health economies applied such a switch strategy, patients required further titration which resulted in a 4:1 ratio not being met, and therefore cost savings could not be realised.

The SPCs for all the botulinum toxin products were very clear that dosage units were not interchangeable from one product to another and Ipsen deemed it irresponsible to recommend a blanket counter ratio. Ipsen's approach was to educate not only payors (who were not wholly familiar with botulinum toxins), but also clinicians and pharmacists on why cost savings could not be guaranteed based on a single ratio.

The campaign aimed to demonstrate that a single dose ratio could not be applied or replicated across different indications, different patient populations and different injectors with different injection techniques. The two leavepieces in question supported the aim of the campaign by highlighting and demonstrating the variation in dose with regard to the regulatory approved SPC dosages for the three BoNT-A products on the market and the publications on dose ratios. Furthermore Ipsen submitted that the intention of the leavepieces was in line with the ruling in Case AUTH/23870/1/11 (Merz v Allergan) which stated that 'the claim that no set dosing ratio has been established is a not unreasonable reflection of the totality of the evidence and that this claim is not misleading and is capable of substantiation'. Ipsen submitted that its aim with the two leavepieces was to reinforce this message to prescribers ie that the dosing units for the different botulinum toxins were not interchangeable and that there was no set dosing ratio between the different toxins; the two themes, of course, were entirely related.

Ipsen stated that it very clearly briefed both leavepieces to the sales team and spent significant time training the team on how to use the materials appropriately. The briefing presentation used at the mid-cycle meeting in April 2013 was provided.

Ipsen stated that Merz appeared not to have conducted the process to date within the spirit of, and to the letter of, the Code. Merz failed to inform Ipsen when it complained to the PMCPA. In addition a non-linear dose-response, as mentioned by Merz was different to a dose ratio and this terminology was not used or referred to during inter-company dialogue. Ipsen did not use this terminology and was unclear as to why Merz had alleged that it had conveyed such a message.

During the inter-company teleconference, Ipsen explained the intention of the leavepieces in question and asked Merz for constructive input into what it would like to see changed. Merz did not offer any suggestions at this stage. Ipsen however clarified, and gained acceptance from Merz, that if 'technical breaches' of the Code were ruled, it would not impact the fundamental message conveyed by the leavepieces which was that a single dose ratio

could not be applied across different indications and health economies. Ipsen stated that it took its responsibilities under the Code very seriously and was frustrated that it was unable to conclude inter-company dialogue with some positive outcome, as Merz accepted that the message would be unaffected by the outcome of a complaint.

A 'Comparison of SPC Doses' leavepiece

This leavepiece set out the various indications for botulinum toxin treatment and tabulated the SPC doses for Dysport, Botox and Xeomin. The last column of the table was headed 'Dose ratios' and where relevant the dose ratios were given for, *inter alia*, Dysport:Xeomin.

1 Misleading extrapolation of data from the SPC

COMPLAINT

Merz submitted that regulatory studies designed for the approval of a product often compared the product under evaluation with another already marketed product, such as in the case of Xeomin for the indication of cervical dystonia which was compared with Botox. Alternatively, for emerging indications products were often compared to the existing standard of care plus placebo, as in the case of the upper limb spasticity licence for Dysport. These studies, when replicated across a number of products in a class, often used different primary and secondary efficacy endpoints and were consequently not suitable source material for an indirect comparison and as such breached Clauses 7.2, 7.3 and 7.4.

The SPC for a particular product contained information from studies designed specifically for that particular product. This was reinforced by European Commission Guidelines on SPCs which stated under the 'Principles of Presenting Information' that:

> 'The SPC provides information on a particular medicinal product; therefore it should not include reference to other medicinal products (e.g. through statements such as 'Like other medicines of the same class…') except when it is a class warning recommended by a competent authority.'

Merz stated that it was clear from this guidance that each regulatory study stood alone and could not be assumed to be appropriate for comparison with another product in its class purely because it had contributed to the granting of the same or similar indication as another product.

Merz therefore considered that it was unacceptable and misleading to derive dose ratios and make indirect comparisons between products purely on the basis of their listing in an SPC. Breaches of Clauses 7.2 and 7.3 were alleged.

To support its allegation Merz highlighted the differences in design of the registration trials for Dysport and Xeomin for their respective licences in upper limb spasticity (ULS). These registration studies were used to inform Section 4.2, Posology and method of administration, of the respective SPCs. Merz summarised the different endpoints and treatment protocols used in these studies:

Xeomin's ULS registration study, Kanovsky *et al* (2009)
- Primary endpoint:
  - response (defined as a ≥1 point improvement in Ashworth Score) for wrist flexors at week 4
- Treatment protocol:
  - required the mandatory treatment of muscles involved with wrist flexion (to ensure the primary endpoint could be credibly analysed), however up to 13 muscles in total could be treated, dependent on the clinical pattern of spasticity.
  - this led to the increased response in secondary endpoints, and also a higher maximum dose, because more muscles were treated
  - outcomes: primary and secondary endpoints were met

Dysport's ULS Registration study, Bakheit *et al* (2001)
- Primary endpoint:
  - the best change from baseline in Modified Ashworth Score (out of the elbow, wrist or finger joints) at week 4
  - the Modified Ashworth Score was a different scale to the Ashworth Score used in Kanovsky
- Treatment protocol:
  - required the mandatory treatment of 5 specific muscles. No other muscles could be treated, therefore limiting the maximum dose
  - outcomes: primary endpoint met, but many secondary endpoints were missed.

Merz noted that the use of indirect comparisons from different studies was tested in Case AUTH/2199/1/09, where the Panel ruled breaches of Clauses 7.2 and 7.3. The Panel ruled on the use of three different studies presented in such a way so as to invite the reader to compare different trial endpoints by placing the trials in a single box. To the right-hand side of the boxed graphs was a short description of the primary endpoints of each study. The endpoints were not the same for each trial. The references for the four different studies were not given with the endpoints, nor anywhere else on the page. Below the description of the endpoints was the statement 'NB: Caution should be exercised when using indirect comparisons across trials'. In the Panel's view this statement did not negate the incorrect implication that an indirect comparison of the data was valid.

In the present case (Case AUTH/2778/7/15) Merz stated that not only did Ipsen tabulate the initial and maximum doses recommended in the individual product SPCs, which invited readers to directly compare the registration dosages and assume equivalent or materially similar outcomes would be achieved, it went further because it wrongly extrapolated these data in the form of a dosage ratio. Merz alleged that the presentation of the data in this manner was misleading in breach of Clauses 7.2 and 7.3. There was no statement to caution the reader

that the endpoints of the registration studies might be different or that indirect comparison might not be advisable or warranted.

Merz stated that in its view, Ipsen's commercial aim was to cause confusion, or imply some form of non-linear/unpredictable dose response between BoNT-A products. By constructing a table of dose ratios by extrapolating data which were fundamentally not suitable for comparison, the implicit claims of the item could not be substantiated and were misleading. Merz alleged breaches of Clauses 7.2, 7.3 and 7.4.

RESPONSE

Ipsen submitted that the leavepiece was designed to demonstrate that even when the dosages as presented in the three SPCs (Dysport, Botox and Xeomin) were compared the derived ratios varied across indications and even differed between initial and maximum doses within the same indication. The leavepiece thus supported the message that a single dose ratio could not be applied in a blanket fashion.

Ipsen submitted that the content and intention of the leavepiece was set out clearly and accurately in the heading ie that doses as stated in the SPCs were compared and not the registration studies as alleged. The registration studies, regardless of age or phase, were the basis for the marketing authorization and the terms of the SPC; the fact that the studies were of different designs or to different standards did not impact at all on the legal conditions embodied in the product licence. Ipsen stated that it was clear from the outset that it had not compared or intended to compare the registration studies for the three medicines, however SPC doses as approved by the regulatory authority for the three products were compared where possible. The wording on the three SPCs were not entirely consistent and Ipsen strove to compare like-for-like where possible to demonstrate the challenge. Where the SPC wordings were significantly different, Ipsen ensured that this was clear in the table, in accordance with the supplementary information to Clause 7.2.

The subheading of the leavepiece clearly stated that the ratios were derived from the SPC, and that the piece was intended to highlight the variation in dose ratios across indications. The piece did not and was not intended to recommend a single fixed ratio. It was stated in bold above the table that botulinum toxin units were not interchangeable and prescribers were advised to consult the products' SPCs for full prescribing information.

The heading made it clear from the outset that the intention of the leavepiece was to highlight the variation in dose ratios across indications; it did not 'invite the reader to make a direct comparison of the registration dosages and assume equivalent or materially similar outcomes would be achieved' as alleged by Merz. Ipsen submitted that the leavepiece contained factual, regulatory approved, information on recommended initial and maximum doses from the SPCs for Dysport, Botox and Xeomin.

Ipsen noted Merz's concerns with regard to comparing regulatory studies, but noted that the leavepiece did not directly, or indirectly, compare or refer to the regulatory studies for the three products and therefore Ipsen submitted that the leavepiece was not in breach of Clauses 7.2, 7.3 and 7.4 on the basis of an inappropriate comparison of regulatory studies as alleged by Merz.

In Ipsen's view the European Commission Guidelines on Summaries of Product Characteristics presented by Merz covered the principles of presenting information within a single SPC and had no bearing on comparing information stated in one SPC with another.

With regard to Case AUTH/2199/1/09, Ipsen stated that the company found in breach had actually compared three different studies inappropriately (as graphs) and was ruled in breach. That case had no bearing on the matter in hand as Ipsen's leavepiece did not contain any direct or indirect comparison of the data contained within the regulatory studies.

Ipsen agreed that comparisons should only be made on a like-for-like basis; therefore, given that the SPCs, at least in terms of dosing guidelines in Section 4.2, reflected the highest level of clinical trial evidence available to the regulatory authority and that the indications for the three products were identical in some instances (which indicated that the MHRA believed that the condition listed eg blepharospasm, represented a single, defined clinical entity rather than a spectrum) it was not unreasonable to deduce a putative dose ratio or range of ratios based purely on the SPCs as it further underlined the non-interchangeability of the toxins.

Ipsen noted Merz's allegation that by tabulating the initial and maximum doses recommended in the individual SPCs, Ipsen had 'invited readers to directly compare the registration dosages and assume equivalent or materially similar outcomes would be achieved'. However, Ipsen submitted that it had presented factually accurate information from the three SPCs in order to demonstrate to prescribers that the SPC dosages should not be directly compared by highlighting the variation in dose ratios across the indications.

Ipsen submitted that the leavepiece accurately reflected the current SPCs for all toxins. It did not mislead and was, for the most part, a matter of fact. The only derived ratio was one deduced directly from the SPCs themselves, so there was no breach of Clause 7.2.

Ipsen noted that Clause 7.3 related to comparisons and submitted that as the majority of the leavepiece was taken directly from the SPCs and the medicines were intended for the same purpose with relevant features ie the initial and maximum recommended doses being compared, there was no breach of this clause.

The information in the leavepiece was taken directly or derived directly from the SPCs, which were referenced, and therefore Ipsen denied a breach of Clause 7.4.

PANEL RULING

The Panel noted that Dysport and Xeomin were both presented in vials containing varying units of botulinum toxin. The Dysport SPC stated that the units of Dysport were specific to that preparation and were not interchangeable with other preparations of botulinum toxin. Similarly, the Xeomin SPC stated that due to unit differences in the LD50 assay, Xeomin units were specific to Xeomin. The Panel considered that this presented a problem to prescribers should they ever need or want to switch a patient from one BoNT-A product to another. The Panel noted that inter-company dialogue showed that Ipsen believed that during the tendering process, Merz had on more than one occasion proposed that a blanket 4:1 switch from Dysport units to Xeomin units, regardless of indication, would be clinically appropriate and offer economic benefit. In that regard the Panel noted that Xeomin was not licensed for all of the same indications as Dysport.

The Panel considered that the leavepiece at issue clearly compared the dosage information taken from the SPCs for Dysport, Botox and Xeomin. SPC dosage particulars were of course derived from registration studies but the Panel did not consider that the leavepiece was a comparison of these studies *per se* as alleged. In that regard the Panel ruled no breach of Clauses 7.2, 7.3 and 7.4 of the Code. The Panel noted that the leavepiece was produced in order to counter a claim that a dose ratio of 4:1 could be applied across the board when changing patients from Dysport to either Botox or Xeomin. In terms of recommended initial doses of shared indications for Dysport and Xeomin, only one dose ratio was stated in the leavepiece ie 1.6:1 for the treatment of blepharospasm. In terms of maximum doses for the two medicines (see Point 2 below) dose ratios of 3.3:1 and 2.4:1 were given for cervical dystonia and for blepharospasm respectively. This countered a blanket switch at 4:1. Nonetheless, in the Panel's view, the final column appeared to give unequivocal, recommended Dysport:other BoNT-A dose ratios for each of the five indications listed. In the Panel's view this was misleading as each ratio given was based on an indirect comparison of SPC dosage particulars for Dysport and the other medicine, not on a head-to-head clinical study of the two. Breaches of Clauses 7.2 and 7.3 were ruled. The claims could not be substantiated; a breach of Clause 7.4 was ruled.

2 Inappropriate use of maximum licensed doses

COMPLAINT

Merz stated that a dose ratio was a comparison between the doses of two medicines. The clinical purpose of providing a dose ratio was generally to identify a dose-response relationship between different medicines and provide guidance when changing from one to another.

The maximum licensed dose of a medicine was usually a measure of the safety/toxicity profile of that particular medicine. When presenting comparative ratios or maximum dosages it was important to consider that as a consequence of switching from one medicine to another, an unsafe dosage of the new medicine might be administered. Merz alleged that to ignore the potential consequences of switching products at the maximum dosage did not encourage the rational use of medicine in breach of Clause 7.10. An illustration of this risk was presented below from the 'Cervical dystonia' section of the table:

In the table, a maximum dose of 1,000 units of Dysport, a maximum dose of 300 units of Xeomin, and the resultant dose ratio of 3.3:1 (Dysport:Xeomin), was presented. These data were derived from the Section 4.2 of the SPCs which were reproduced below:

Dysport: 'Doses within the range of 250-1000 units are recommended, although the higher doses may be accompanied by an increase in side effects, particularly dysphagia. The maximum dose administered must not exceed 1000 units.'

Xeomin: 'Normally, in practice, the total dose administered does not exceed 200 units. Doses of up to 300 units may be given.'

Merz concluded that in normal circumstances the maximum dosage for Dysport and Xeomin would be 1000 units and 200 units respectively. Given the established safety risks associated with overdose on BoNT-A preparations, and the clear guidance in Section 4.4 Special warnings and precautions for use of the Xeomin SPC outlined below, the difference between 'normal' and 'unusual' practice could be considered very important.

> 'Undesirable effects related to spread of Botulinum toxin distant from the site of administration have been reported (see section 4.8), sometimes resulting in death, which in some cases was associated with dysphagia, pneumonia and/or significant debility.'

By presenting a dosage conversion of 3.3:1 (Dysport:Xeomin) the leavepiece invited physicians to consider a patient receiving a dosage of 750-1000 units of Dysport (recommended range of 250-1000 units), to require 227-300 units of Xeomin should they be switched. These figures were well above the normal recommended dosage of 200 units of Xeomin. No clear warning or guidance about the actual SPC wording or implications was given. Merz alleged that the derivation of dose ratios through extrapolation of data which was not suitable for comparison, presented an incomplete analysis, was fundamentally misleading, did not encourage rational use and was not in the interest of patient safety. Merz thus alleged a breach of Clause 7.10.

RESPONSE

Ipsen submitted that the leavepiece accurately reflected the current SPCs for all toxins and accurately described the derivation of the ratios.

Ipsen agreed with Merz that the studies that informed the SPC were designed for each particular product and conducted in different eras and under

different conditions but led to a common regulatory inclusion in the product licenses. The two commonly used measures of efficacy and toxicity were the 'minimum effective dose', which gave an indication of the dose below which no meaningful clinical effect was seen, and the 'maximum tolerated dose' above which tolerability or safety issues outweighed any clinical benefit. Therefore the therapeutic window for any given product was defined by these two parameters. For the toxins in question, these had been translated into Section 4.2 of the SPCs as the recommended initial and maximum doses.

The leavepiece was not designed or intended to recommend a dose ratio and did not encourage inappropriate use of any of the medicines. The purpose was to encourage rational use of the toxins and discourage the use of a single dose ratio across indications and populations. Ipsen submitted that patients could be harmed if a single dose ratio was applied across an entire health economy. Therefore, Ipsen denied a breach of Clause 7.10.

PANEL RULING

The Panel noted its comments above at Point 1 and its view that the final column of the leavepiece appeared to give unequivocal, recommended Dysport: other BoNT-A dose ratios for each indication listed. With regard to the treatment of cervical dystonia the Panel noted that the Xeomin SPC stated that the total dose administered did not usually exceed 200 units but that doses of up to 300 units might be given. The leavepiece at issue however stated, without explanation, that the recommended maximum dose of Xeomin was 300 units. The maximum recommended dose for Dysport in the treatment of cervical dystonia was simply stated to be 1000 units although the SPC stated that whilst doses within the range of 250-1000 units were recommended, the higher doses might be accompanied by an increase in side effects, particularly dysphagia. The resultant dose ratio for Dysport:Xeomin at the maximum dose of each was stated to be 3.3:1. Overall the Panel considered that the references to the maximum doses of Dysport and Xeomin in the leavepiece did not accurately reflect the information given in the SPC or even alert the reader that more details in particular about side effects should be sought. In that regard the Panel did not consider that the statement at the top of the table that the products' SPCs should be consulted for full prescribing information was sufficient. In the Panel's view, the simplistic way in which the information had been presented did not encourage the rational use of the medicines. A breach of Clause 7.10 was ruled.

B 'Botulinum Toxins – The Ratio Challenge' leavepiece

Table 1 of the leavepiece detailed the results of a systematic review of clinical studies which were conducted to determine or test an hypothesised dose ratio between Dysport, Xeomin and Botox. Table 2 presented data from studies published after the systematic review was conducted (February 2012).

1 The leavepiece did not reflect the balance of evidence, and was out of date

COMPLAINT

Merz was concerned that claims in the leavepiece were misleading and did not reflect the balance of evidence in breach of Clause 7.2. By providing an incomplete analysis of the data, Ipsen had deliberately failed to represent publications which conflicted with its message.

Merz stated that readers would base their judgement on the summary of the methodology and description of the inclusion criteria for the meta-analysis shown on the front page of the leavepiece:

> 'A systematic review … aimed to retrieve all relevant published studies that report data conducive to the determination of a dose equivalence ratio of Dysport in comparison to Botox and Xeomin …'
>
> '77 studies were identified … reviewed to find studies which specifically aimed to either determine a dose ratio or test a hypothesised dose ratio between Dysport and Botox or Xeomin. There was no restriction by study design and therefore both prospective and retrospective studies were included.'
>
> '11 studies relevant to this analysis approach were identified and are reviewed in Table 1. A further study, published after the review, is included in Table 2.'

Merz stated that at least two studies (Cossar and Cozens 2015 (abstract/poster) and Grosset *et al* 2015 (publication)) which involved Dysport and Xeomin would meet the above criteria and could have been included in Table 2 as 'further studies'. Breaches of Clauses 7.2 and 7.3 were alleged.

RESPONSE

Ipsen explained that it instigated a systematic review which was conducted in February 2012 by a life sciences consultancy. The findings of this review were presented in the leavepiece now at issue, 'Botulinum Toxins – The Ratio Challenge'. With biologicals, such as botulinum toxins, dose ratios were very complicated and subject to inherent variation. The leavepiece was designed to demonstrate this inherent variation and to remind the customer of all the factors that could influence a perceived ratio. The section of the leavepiece headed 'The Dose Equivalence Ratio Questions:' was intended to challenge a customer's perception on the existence of a fixed dose ratio and to determine if there was any change following a discussion of the data. Ipsen was frequently asked to provide a specific equivalence or switch ratio as it would simplify cost comparisons and the tender process so it needed materials to allow the field force to explain the complexity of issues surrounding a potential switch and highlight the lack of interchangeability between the products.

Ipsen noted Merz's concern that two recently published studies (Cossar and Cozens and Grosset *et al*) were not included in the systematic review. This was because when the systematic review was conducted in February 2012, neither study had been

published. The more complex question was whether or not these two studies (and any other relevant studies published after February 2012) altered the balance of evidence from the systematic review.

The systematic review identified 77 studies which were screened and required to meet pre-defined eligibility criteria. Eleven studies met these criteria and were the subject of the leavepiece, with one further study published after the systematic review was completed in 2012, but meeting all the eligibility criteria, included as a separate item.

Ipsen submitted that the leavepiece summarised key details from the 12 studies and posed a series of questions on dose ratio – which were not answered *per se*. In fact, the leavepiece made no real claims at all although it did report on the 'clinically equivalent dosing ratio' stated in each study. It was clear from these that there was not a fixed, or set, dosing ratio between toxins (therefore again in line with Case AUTH/2380/1/11). Even if Cossar and Cozens and Grosset *et al*, assuming they met the eligibility criteria for the systematic review, were included, this would only add another potential ratio; it would not 'set' the ratios to a single figure. Ipsen noted that Cossar and Cozens was published in March 2015, a month before the initial inter-company complaint was received in April 2015 despite the fact that the leavepieces at issue had been used since March 2013, and were re-approved following an update to the prescribing information in January 2014.

Ipsen stated that the systematic review was repeated in September 2014 with 106 studies now identified, of which 16 met the eligibility criteria. The conclusions had not changed, with no consistent dosing ratio identified between Dysport and other BoNT-A products either across different indications or for any of the single indications assessed.

Ipsen noted Merz's suggestion that the two studies published in 2015, for which Merz provided editorial funding, could now be added to Table 2 in the leavepiece. Ipsen was concerned that Merz did not proffer inclusion of the two 2015 studies in the leavepiece during inter-company dialogue when asked what amendments to the leavepiece would satisfy Merz. However Ipsen stated it would need to ensure that the studies – and any other relevant studies – met the pre-defined criteria set in the meta-analysis design.

Ipsen maintained that the message of the leavepiece would not change with the addition of the two publications, as the 4:1 ratios concluded in these publications simply added to the plethora of ratios already published and would strengthen the argument that a single, fixed ratio could not be recommended or achieved across different indications.

Ipsen submitted that the leavepiece was an accurate and up-to-date reflection of the evidence available and it therefore denied breaches of Clauses 7.2 and 7.3.

PANEL RULING

The Panel noted that the leavepiece at issue presented the results of a systematic review in February 2012 of the published data that was able to show a dose equivalence ratio for Dysport in comparison to Botox and Xeomin. Seventy-seven studies were identified of which 11 met the eligibility criteria. At the time, no relevant studies were identified which compared Dysport and Xeomin and so the data presented in the leavepiece only related to Dysport and Botox. The Panel noted Ipsen's submission that a subsequent systematic review conducted in September 2014 identified 106 studies, of which 16 met the eligibility criteria. In early 2015 two studies (both with editorial support from Merz) had been published which had looked at switching from Dysport to Xeomin at about a 4:1 dose ratio (Grosset *et al* and Cossar and Cozens); it appeared that Grossett *et al* had been published electronically ahead of print in October 2014. Merz submitted that these studies would meet the eligibility criteria set for the systematic review conducted in 2012 although Ipsen was not certain on that point. The Panel noted that both Grossett *et al* and Cossar and Cozens concluded that when switching patients from Dysport to Xeomin the dose ratio was approximately 4:1. The Panel noted that the leavepiece was part of a campaign to dispel claims that there was a blanket 4:1 dose ratio for Dysport:other BoNT-A products. Inter-company dialogue showed that Ipsen believed that during the tendering process, Merz had on more than one occasion proposed that a blanket 4:1 switch from Dysport units to Xeomin units, regardless of indication, would be clinically appropriate and offer economic benefit. The Panel noted Ipsen's submission, however, that it was anecdotally aware that where clinics or health economies applied such a switch strategy, their patients required further titration which resulted in a 4:1 ratio not being met, and therefore cost savings could not be realised. The Panel further noted that Xeomin was not indicated for all of the same indications as Dysport.

The Panel noted that the leavepiece (dated January 2014) detailed a meta-analysis conducted in February 2012; it had not been updated to reflect the meta-analysis conducted in September 2014 and nor did it include data on Dysport:Xeomin which had since been published. The front page of the leavepiece clearly stated that 'no studies compared Dysport and Xeomin'. In so much as it did not detail the 2014 meta-analysis (even assuming that neither Grossett *et al* nor Cossar and Cozens met the eligibility criteria) the Panel considered that the leavepiece was not based on an up-to-date evaluation of all the data. A breach of Clause 7.2 was ruled. In the Panel's view, readers would assume that all of the relevant data had been included which was not so. In that regard the comparisons made were misleading and a breach of Clause 7.3 was ruled.

2 The use of both leavepieces together

COMPLAINT

Merz stated that the use of leading questions, 'Does a single dose ratio exist?', 'Does a dose ratio exist at an individual patient level?' etc was controversial, as it did not know how Ipsen representatives were briefed to use this item.

If the two leavepieces were used in association with one another, the leading questions asked by 'The

Ratio Challenge' leavepiece could be answered by the 'Comparison of SPC Doses' leavepiece, which provided a seemingly random set of dosage ratios for each indication. In this instance the absence of evidence that a single fixed dosing ratio existed could not be equated to proof that a fixed dosage ratio did not exist.

Therefore Merz alleged that this leavepiece, and particularly the way it would be used, breached all the above clauses stated for the previous 'Comparison of SPC Doses' leavepiece. Breaches of Clauses 7.2, 7.3 and 7.10 in this regard were alleged.

RESPONSE

Ipsen noted that Merz's view that the question 'Does a dose ratio exist at an individual patient level?' was controversial did not make it in breach of the Code. Indeed, the questions within the leavepiece were designed to be thought-provoking and to emphasise the controversy that existed.

Ipsen was confident that the sales team briefing on both leavepieces was sufficiently robust to ensure appropriate and responsible use. Indeed, the two leavepieces were designed to be used together. The question to the reader was, based on the variation in dose ratios demonstrated by comparing the SPCs and based on a robust systematic review; did the reader believe that a single dose ratio could be replicated within a health economy, across a range of indications, treated by multiple injectors?

As the briefing document was commercially confidential, Ipsen provided the following summary. The sales team was briefed to ask 'The Dose Equivalence Ratio Questions', before discussing the data contained within the leavepieces, but not to answer or discuss these questions in depth.

Representatives would then discuss the data from the systematic review and Table 2, and from the SPCs, and highlight the variation in dose ratios across and within indications. They then closed the conversation by referring back to the questions to check whether or how the data had changed the customer's perception with regard to dose ratios.

In relation to Merz's comment 'In this instance the absence of evidence that a single fixed dosing ratio exists could not be equated to "proof" that a fixed dosage ratio does not exist.', Ipsen submitted that the leavepieces did claim that a fixed ratio did not exist on a population basis. A fixed ratio might exist for a single patient with a specific condition, treated by a single injector, but – as amply demonstrated – it had thus far eluded substantiation. As stated before, the question that these leavepieces aimed to address was whether (based on the published literature and SPCs) a single fixed ratio could be applied or replicated across an entire health economy and whether it was appropriate to base claims on cost savings on this assumption.

Ipsen submitted that the sales team had been adequately briefed and that using the two leavepieces together was not in breach of Clauses 7.2, 7.3 and 7.10.

PANEL RULING

The Panel noted that the representatives' briefing material (April 2013) for the leavepiece detailed two key points. The first point was that there were no publications comparing Dysport and Xeomin and as part of that point there was no evidence base supporting a ratio and SPCs were the only comparison and guidance. The Panel noted that the claim that there were no publications comparing Dysport and Xeomin was now out-of-date; Grossett *et al* had been published electronically in October 2014 and in hard copy in early 2015 and Cossar and Cozens was published in March 2015. The reference to the SPCs providing the only comparison and guidance would, in the Panel's view, on the balance of probabilities lead to a discussion of the 'Comparison of SPC Doses' leavepiece, at issue in Point 1 above. In that regard the Panel considered that the two leavepieces were inextricably linked and that its rulings at Point 1 above of a breach of Clauses 7.2, 7.3 and 7.10 applied to their combined use.

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During its consideration of this case, the Panel was concerned to note that inter-company dialogue showed that Ipsen believed that during the tendering process, Merz had on more than one occasion proposed that a blanket 4:1 switch from Dysport units to Xeomin units, regardless of indication, would be clinically appropriate and offer economic benefit. In that regard the Panel noted that Xeomin was not licensed for all of the same indications as Dysport. The Panel further noted Ipsen's submission that anecdotally it knew of reports where a 4:1 switch strategy had been used with the result that patients required further titration and the anticipated cost savings were not realised. The Panel queried whether Cossar and Cozens and Grossett *et al* were robust enough to base a blanket claim of a 4:1 dose ratio Dysport:Xeomin regardless of the indication. The Panel requested that Merz be advised of its concerns in this regard.

Complaint received **7 July 2015**

Case completed **3 September 2015**