CASE AUTH/3228/7/19

MERZ v IPSEN

Promotion of Dysport

Merz Pharma UK Ltd submitted a complaint about the promotion of Dysport (clostridium botulinum type A toxin) by Ipsen UK Ltd. Dysport was indicated for the symptomatic treatment of focal spasticity in certain limbs and for symptomatic treatment of certain spasms.

Merz's product, Xeomin (clostridium botulinum neurotoxin type A) was indicated for the symptomatic treatment of certain spasms and chronic sialorrhea due to neurological conditions.

Merz stated that it entered inter-company dialogue with Ipsen regarding activities and materials including that claimed superior efficacy of Dysport, with relation to duration of effect. Merz alleged such claims were incapable of substantiation and were misleading. Ipsen conflated *post hoc* analyses of injection intervals with claims of increased product potency. Merz was satisfied that the concerns raised had been addressed and drew the inter-company dialogue to a close.

Merz stated that despite the undertakings by Ipsen UK during the inter-company dialogue, healthcare professionals had continued to raise concerns with Merz that Ipsen UK maintained a committed strategy of differentiation on a platform of sustained duration of effect and that this was pervasive throughout Ipsen's activities. The reports of the continued promotion came from three named hospitals across the country. An example of the current activity came from a named senior hospital pharmacist in relation to a recent discussion with Ipsen regarding Dysport and Xeomin, led by a senior Ipsen employee, where it was argued that the trust was disadvantaging its patients by using an inferior product, Xeomin, rather than Dysport which had a longer duration of effect. The consequence of this practice meant that patients were missing out on the superior product and the trust was running unnecessary clinics, and consequently wasting resource. Promotional material was offered, referencing claims from a US study, supporting these arguments which was declined as the pharmacist believed the claims to be misleading, in light of the trust's direct experience in previously switching from Dysport to Xeomin.

The detailed response from Ipsen is given below.

The Panel noted Ipsen's submissions regarding the SPC for Dysport and intervals between treatments which varied according to the indication. Dysport was not to be used more frequently than every 12 weeks, some indications were for use at 12-16 weeks or longer, another was approximately every 16 weeks or as required to maintain a response. For focal spasticity of upper limb clinical improvement might last up to 20 weeks. The data provided by Merz and Ipsen compared Dysport with placebo in various

indications. No data was submitted by either Merz or Ipsen comparing the efficacy of the various toxins. It appeared that there were no comparative data.

The Panel noted that the claims 'Dysport extends time to retreatment in some patients' and 'Dysport offers sustained effect of treatment up to 24 weeks in some patients for upper and lower limb spasticity' were the subject of inter-company dialogue and that Ipsen confirmed that materials with these claims would be withdrawn. Ipsen submitted that it reserved the right to present clinical data within licence covered in the Dysport SPC.

Merz referred to activities in three different geographical areas following the closure of inter-company dialogue. Little detail had been provided. Ipsen acknowledged there had been a meeting with one senior hospital pharmacist where employees discussed pricing issues and commercial terms. Ipsen submitted that the employees present were aware of the inter-company dialogue with Merz and had received briefing material. The Panel noted that this briefing material did not refer to the inter-company dialogue but did state in bold, 'When discussing Dysport, it is important no comparison should be made with other toxins as we do not have any prospective head to head studies'. In relation to the two other geographical areas, Ipsen submitted that it had no evidence that any discussions had taken place regarding 'sustained duration of effect' as alleged.

The Panel considered that there was little evidence provided by Merz that representatives' conversations demonstrated that Ipsen promoted 'differentiation on a platform of sustained duration of effect' and in particular that Dysport had a longer duration of effect than Xeomin as alleged. The Panel considered that given the material which was withdrawn as a result of inter-company dialogue it was not unreasonable that some employees might consider that the previous claims that Dysport extended time to retreatment and offered sustained effect of treatment was a reason for choosing Dysport in preference to other toxins. Further the representatives had not been told in the briefing document that materials with these claims had been withdrawn following inter-company dialogue. Representatives were told that the material was withdrawn in readiness for a prescribing information update.

Ipsen provided some pages from its current materials and the associated representative briefing documents. Time to retreatment with Dysport from the open-label extension phase of studies in adults with upper limb and lower limb spasticity featured in materials. The associated briefing documents stated, 'No direct comparisons should be made to other toxins in the absence of head to head studies'. There was no complaint about Ipsen's new material. The claims that Ipsen agreed to withdraw following inter-company were not within the pages of the current materials provided by Ipsen.

The Panel considered that Merz had not shown on the balance of probabilities that Ipsen employees had promoted at the three named hospitals that Dysport had a longer duration of effect than other toxins or that it promoted differentiation on a platform of sustained duration of effect as alleged. It therefore ruled no breaches of the Code including in relation to high standards. These rulings were appealed by Merz.

On appeal Merz alleged that Ipsen in its promotion of Dysport had continued (after the conclusion of apparently successful inter-company dialogue in 2018) to promote

messages that created an unsubstantiated and misleading impression of superior duration of effect of Dysport (relative to competitor toxins) to UK health professionals.

Merz provided detailed comment to help the Appeal Board to understand the validity of the clinical data on which Ipsen sought to find its claims.

Merz alleged that despite a successful inter-company dialogue reports from customers of a continuance of the duration of effect campaign were maintained. Whilst disappointing it was not altogether unsurprising given this activity would bring Ipsen UK in line with what was clearly a global campaign, with similar claims still reflected in global corporate materials and symposia.

Merz directed the Appeal Board to a number of points which it summarised in light of the fact that Ipsen failed to brief the sales team that the claims at issue were subject to an inter-company undertaking at the time of withdrawal, that materially similar claims were still in use in the Dysport promotional material, that these claims were demonstrably part of the wider corporate strategy for product differentiation, that Ipsen had a misguided belief that unevidenced claims could be shielded by careful wording of the SPC, and finally that a senior hospital pharmacist had gone on record that these claims continued to be made. Merz alleged that, on the balance of probabilities, Ipsen had continued to promote Dysport through an unevidenced duration of effect claim relative to other BoNTs and in doing so had breached the Code.

Merz alleged that in failing to highlight the inter-company dialogue, which preceded the withdrawal, and include clear guidance for the sales team to discontinue the use of the disputed claims, or similar claims, Ipsen was in clear breach of the spirit of the inter-company dialogue and, by association, the Code. Merz stated that this lack of commitment to follow through on the obligation to brief sales staff tipped the balance of probabilities in favour of continued use of the claims, as reported by the senior hospital pharmacist who provided a statement that the claims continued to be made at a meeting which included a senior member of the Ipsen management team, who Ipsen confirmed was aware of the undertaking, reinforced the lack of commitment to accept the inter-company dialogue as binding.

Merz referred to the Ipsen briefing documents for some of the revised promotional materials following the withdrawal. Within each a heading, 'Dysport – A toxin with a long-lasting effect', gave a clear steer on the purpose of the new materials, namely to differentiate Dysport within the BoNT-A market as a BoNT-A with a long-lasting effect.

Merz stated that a toxin with a long-lasting effect represented a clear comparison to alternative BoNT-A preparations. Given the inter-company dialogue commitment to refrain from duration of effect claims incapable of substantiation it was surprising to see the prominence of the comparative statement in the briefing material. The reason for its prominence was captured below with the bullet: 'This was an important claim to be comfortable with substantiating in call as it is a key message in a lot of messaging around Dysport'.

Merz alleged that this statement implied that there had been some discomfort with the substantiation of the claim within the sales team, it also clearly highlighted the message

'Dysport - a toxin with long-lasting effect' was central to the Ipsen UK commercial strategy. It was the only message reinforced within the new material, which in Merz's view, was completely aligned with an Ipsen global corporate campaign which set out to directly compare the duration of effect of Dysport to that of Xeomin and Botox. Further, given there had been recent and clear undertakings directly relating to claims regarding duration of effect, it was extraordinary that no effort was made to highlight these recent undertakings around the now sensitive duration of effect claims, especially given its absence in the previously cited materials withdrawal briefing.

Merz alleged that, in summary, the additional enclosures provided by Ipsen in its submission and shared with Merz further supported the central argument. Taking these additional insights, and given the written testimony of the senior hospital pharmacist in a meeting that was undisputed to have taken place, it was most certainly now beyond the balance of probabilities that comparative and disparaging statements were made implying a superior duration of effect for Dysport when compared to Xeomin. Taken collectively the repeated misrepresentation of data and the failure to effectively brief the sales team to make them 'comfortable with substantiating these claims' represented a failure in the most basic standards expected of a pharmaceutical company.

The Appeal Board noted that the claims 'Dysport extends time to retreatment in some patients' and 'Dysport offers sustained effect of treatment up to 24 weeks in some patients for upper and lower limb spasticity' were the subject of inter-company dialogue and that Ipsen confirmed that materials with these claims had been withdrawn. Ipsen had not referred to the inter-company dialogue in the briefing material for sales representatives to indicate why the material was being withdrawn. The Appeal Board considered that this would have reinforced to representatives that such claims should no longer be used in line with Ipsen's inter-company agreement.

The Appeal Board noted that Merz had referred to activities in three different geographical areas. The only evidence provided was the email exchange between Merz and a senior hospital pharmacist. The Appeal Board noted that Merz had provided its written account of the interaction between Ipsen and the senior hospital pharmacist based on the pharmacist's account as described to Merz. It was not directly from the pharmacist. The account written by Merz, referred to Ipsen representatives stating that '…the Trust was disadvantaging the patients in its care by using an inferior product, Xeomin, rather than Dysport which it was further argued had a longer duration of effect…'. The pharmacist agreed that Merz had summarised his account of his/her interaction with Ipsen accurately. The Appeal Board noted that Ipsen had no detailed call notes from the meeting and that the Ipsen representatives were adamant that the account was not correct. It was unusual for a senior hospital pharmacist to be involved with a dispute between two pharmaceutical companies.

The Appeal Board noted that the current Ipsen advertising campaign included the claim 'Dysport – A toxin with a long-lasting effect'. There was little explanation provided in the promotional material or the briefing material to explain what was meant by the '…long-lasting effect' and the strength of any supporting data. The purpose of many promotional claims was to differentiate one medicine from another. Whilst the claim might be factual, in the context of a main promotional claim, the Appeal Board considered it would be read in relation to other medicines and was misleading in relation to the undue emphasis on the duration of effect of Dysport with regard to other

neurotoxins. The Appeal Board noted that there had been no head to head studies to show a difference in the duration of effect of any neurotoxins. The Appeal Board also considered that the email from Merz and the senior hospital pharmacist provided evidence that Ipsen representatives had, on the balance of probabilities, been misleading with regard to the implied benefit of Dysport in terms of its duration of effect. The Appeal Board ruled a breach of the Code. The appeal on this point was successful. In this regard the Appeal Board did not consider that it had evidence that the implied benefit of Dysport in terms of its duration of effect amounted to a misleading comparison with Xeomin as alleged and the Appeal Board consequently ruled no breach of the Code. The appeal on this point was unsuccessful.

The Appeal Board considered that, on the evidence provided, the Ipsen representatives had not encouraged the rational use of Dysport and the implied benefit with regards to its duration of effect could not be substantiated and it therefore ruled a further breach of the Code. The appeal on this point was successful.

The Appeal Board ruled a breach as overall, Ipsen had failed to maintain high standards. The appeal on this point was successful.

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Merz's product, Xeomin (clostridium botulinum neurotoxin type A) was indicated for the symptomatic treatment of certain spasms and chronic sialorrhea due to neurological conditions.

COMPLAINT

Merz stated that it entered inter-company dialogue with Ipsen regarding activities and materials that claimed superior efficacy of Dysport, with relation to duration of effect. Merz alleged such claims were incapable of substantiation and that Ipsen conflated *post hoc* analyses of injection intervals with claims of increased product potency.

Merz stated that whilst a number of concerns were addressed during inter-company dialogue, including misleading visuals and promoting outside of the licence through omission, the unsubstantiated and misleading claim of superiority of Dysport in regard to duration of effect was the main focus.

During dialogue related to a leavepiece 'Why choose Dysport?' (ref DYS-UK-002956) Merz alleged that the headline on page 2 '*Dysport* extends time to retreatment in some patients', was a hanging comparison, invited readers to consider a comparison of Dysport to Xeomin or Botox explicitly implying that an extended duration of effect in favour of Dysport had been established. Neither of the two supporting references was a comparative study or compared a period of previous treatment by Xeomin or Botox with a new extended period of efficacy with Dysport. Merz alleged that the claim that Dysport might lead to extended intervals versus alternative formulations of botulinum toxin was ambiguous, unsubstantiated and misleading. Breaches of Clauses 7.2, 7.3, 7.4 and 7.10 and Clause 9.1 were alleged.

Page three of the same item contained the headline 'Dysport offers sustained effect of treatment up to 24 weeks in some patients for upper and lower limb spasticity'. The data presented were

post hoc analyses of two clinical trials which examined the time to reinjection of patients. Within the original trial protocol clinicians had the choice of injecting at the 12 week assessment visit or rolling over to subsequent visits at additional 4, 8 or 12 weeks intervals. In presenting this data, Ipsen strongly implied that the only reason a physician should choose not to reinject at 12 weeks, was that the patient had benefited from symptomatic relief until the next visit, ie for the full 16, 20 or 24 weeks.

This claim, using time of reinjection as a surrogate for efficacy, was presented despite there being no significant difference between placebo and Dysport at week 12 and beyond, against the predefined primary efficacy measure of Modified Ashworth Scale (MAS). Visuals on the page had been laid out to show that the majority of patients had results lasting beyond 12 weeks. However, the original study data showed the majority of patients, 63.2% in upper limb and 79.9% in lower limb, were injected at the 12 week review. Merz argued the *post hoc* analyses and subsequent presentation of the data were clear misrepresentations of the original study data. Merz alleged breaches of Clauses 7.2 and 7.3 (and in the case of the imagery, Clause 7.8).

As a result of the concerns and challenges raised by Merz which concluded in November 2018, Ipsen UK committed to a number of actions including:

- Withdrawal of the leavepiece
- Withdrawal of items with the duration of effect claims, or similar claims, regardless of the type of material or the setting (whether it be promotional or non-promotional)
- Withdrawal of all items with the claim ‘think beyond 12 weeks’
- Withdrawal of all items with the claim ‘Dysport offers sustained effect of treatment up to 24 weeks in some patients for upper and lower limb spasticity’
- Withdrawal of all items with the claim ‘Dysport extends time to retreatment in some patients’
- A brief to the sales and medical science liaison (MSL) teams that in the absence of comparative studies no cross trial comparisons could be made.

Merz was satisfied that the concerns raised had been addressed and drew the inter-company dialogue to a close.

Post-inter-company dialogue promotion

Merz stated that despite the undertakings by Ipsen UK, healthcare professionals had continued to raise concerns with Merz that Ipsen UK maintained a committed strategy of differentiation on a platform of sustained duration of effect and that this was pervasive throughout Ipsen’s promotional and non-promotional activities. The reports of the continued promotion came from across the country from the three named hospitals indicating a clear corporate strategy since these locations covered three separate sales representative territories.

An example of the current activity came from a named senior hospital pharmacist:

> ‘In a recent discussion with Ipsen regarding Dysport and Xeomin, which was led by a senior Ipsen employee, it was argued that the Trust was disadvantaging the patients in its care by using an inferior product, Xeomin, rather than Dysport which it was further argued had a longer duration of effect. The consequence of this practice meant that patients were missing out on the superior product and the Trust was running unnecessary clinics,

and consequently wasting resource. Promotional material was offered, referencing claims from a US study, supporting these arguments which was declined as the pharmacist believed the claims to be misleading, in light of the Trust's direct experience in previously switching from Dysport to Xeomin. Concern has been expressed that these messages could have a destabilising effect on the local health economy providing an unnecessary distraction for an otherwise already busy service.'

In the light of this unsubstantiated promotion Merz alleged breaches of Clauses 7.2, 7.3 and 7.10. The repeat use of claims post-inter-company dialogue undertaking again constituted a breach of Clause 9.1.

RESPONSE

Ipsen stated that as the complaint called into question the interpretation of the actions agreed following the inter-company dialogue, it was disappointing that Merz chose to complain directly to the PMCPA rather than to seek to clarify or re-open the inter-company dialogue. Ipsen stated that it cooperated fully with Merz in 2018 and Merz, being happy with the actions proposed by Ipsen, brought the inter-company dialogue to a close. The action now taken by Merz, not only in raising this complaint without first seeking to re-engage with Ipsen, but in raising this complaint primarily on the basis of an undocumented comment by a single healthcare professional, was surprising. Nevertheless, it welcomed the views of the PMCPA as to Ipsen's conduct in relation to the inter-company dialogue and subsequently.

Background

In the inter-company dialogue, Merz challenged certain aspects of Ipsen's sales, marketing and medical activities and materials. The focus of the complaint was a leave piece (DYS-UK-002956) 'Why Choose Dysport'.

Given the focus of Merz's complaint related to duration of effect claims, the company included extracts from the leavepiece 'Why Choose Dysport' and the parties' correspondence.

To take each of these claims in turn:

1 'Dysport extends time to retreatment in some patients' (the 'Extends Time to Retreatment Claim').

As noted in the inter-company dialogue, Ipsen did not intend this statement to draw a comparison with any other product; indeed, no other products were mentioned in the leavepiece. Nevertheless, to make this point absolutely clear, Ipsen confirmed it would no longer use this claim in its current form.

2 'Dysport offers sustained effect of treatment up to 24 weeks in some patients for upper and lower limb spasticity' (the 'Sustained Effect Claim').

Ipsen disagreed with Merz that this claim was misleading. Ipsen maintained that this overarching claim in the original material in question was supported by the display of percentages clearly within the leavepiece (with the total number of patients). Nevertheless, to avoid any further misinterpretation, on 30 November, Ipsen agreed to:

> 'the immediate withdrawal of all items with the above claim highlighted, or similar claims in Ipsen's promotional and non-promotional materials which was an action already taken when Ipsen responded to Merz on 1 November 2018….'

However, Ipsen also clarified at this point that it reserved the right to present Dysport clinical data within the licence covered in the Dysport summary of product characteristics (SPC).

Ipsen stated its letter of 30 November ended with a summary of the actions Ipsen agreed to take as a result of the inter-company dialogue in the interests of avoiding any further misinterpretation, and to demonstrate Ipsen's commitment to maintaining high standards. In terms of the actions relating to the two highlighted claims above, these were:

1 The immediate withdrawal of all items with duration of effect claim highlighted, or similar claims, including: leavepieces, economic models, slide sets, electronic sales aids or items in any format including promotional and non-promotional materials.
2 The immediate withdrawal of all items with the claim 'Think beyond a 12-week injection' highlighted, or similar claims, including: leave pieces, economic models, slide sets, electronic sales aids or items in any format including promotional and non-promotional materials.
3 To ensure that no further items with the following claims remained in circulation:
   'Dysport offers sustained effect of treatment up to 24 weeks in some patients for upper and lower limb spasticity'
   'Dysport extends time to retreatment in some patients'.
4 To ensure that all licensed indications were sufficiently prominent in any replacement materials.
5 To reinforce to the Dysport sales and MSL team that all activities must be in accordance with the Code and that, in the absence of comparative studies, no cross-trial comparisons could be made.

Other commitments were also made but these did not relate to the 'Extends Time to Retreatment' claim nor the 'Sustained Effect' claim referred to above.

In relation to 'the immediate withdrawal of all items with duration of effect claim highlighted, or similar claims, (point 1) this was in reference to the 'Sustained Effect' claim 'Dysport offers sustained effect of treatment up to 24 weeks in some patients for upper and lower limb spasticity' in the original leave piece in question. Ipsen maintained that this overarching claim was supported by the display of percentages clearly (with the total number of patients) but in order to avoid any further misinterpretation of the claim in question, Ipsen made a decision on the immediate withdrawal of all items with the above claim highlighted, or similar claims in Ipsen's promotional and non-promotional materials.

It should be noted at this point that Ipsen had anticipated replacing the leavepiece (DYS-UK-002956) 'Why Choose Dysport' in early 2019 when a new campaign would be launched. For this reason, whilst it disagreed with many of the issues raised by Merz in the course of the inter-company dialogue, a key factor in the decision to withdraw the relevant materials etc was that it had planned to do so in the coming months in any event. Further, whilst the company was prepared to agree to the withdrawal of particular materials which related to the specific claims as outlined above under discussion with Merz at the time, at no point did it agree to no longer pursue a campaign which promoted Dysport within its licence and in line with the Code; indeed

it was made clear to Merz that it reserved the right to present Dysport clinical data within licence as covered in the Dysport SPC.

Merz accepted the actions proposed above and, therefore, the inter-company dialogue was closed.

Action taken since inter-company dialogue

As part of the agreement from the inter-company dialogue, Ipsen UK withdrew all the materials in relation to the claims and materials in question, which had been recorded as part of the company withdrawal of materials process:

- 306739-FOR Signed Withdrawal Completion Form for DYS-UK-002956 which was circulated by email to all sales representatives on 24 October 2018
- 306738-FOR Withdrawal Log - 24OCT2018 - which indicated members from the sales team required to return all materials in question for withdrawal
- DYS-UK-003026 Internal briefing on the withdrawal of materials dated 1 November 2018.

It should be noted that the date of withdrawal of materials and subsequent briefing pre-dated closure of the inter-company dialogue as it had already made the decision to withdraw the materials due to the expectation that new materials would follow in early 2019. It was for this reason that the inter-company dialogue itself was not mentioned in the briefing.

Ipsen confirmed that no further materials had been put into circulation to include the 'Extends Time to Retreatment' claim nor the 'Sustained Effect' Claim, nor any similar claims since the inter-company dialogue. Ipsen included all examples of materials approved and in circulation by Ipsen from 1 November 2018 to 24 July 2019 (the date of the complaint letter) which contained statements relating to duration of effect. These were current campaign materials and that it would therefore be inappropriate for Merz a competitor to gain access to these materials. Ipsen requested that these were not shared further without its consent.

Briefing DYS-UK-003026 dated 1 November 2018 was circulated to the commercial field-based team, medical advisor and MSL by the interim head of marketing on 1 November 2018. Between 1 November 2018 and 24 July 2019, Ipsen confirmed that the only representative materials which contain statements relating to duration of effect in circulation for use with customers were:

- Dysport SPC.
- DYS-UK-003026 Internal briefing on the withdrawal of materials dated 1 November 2018 (Appendix 3).
- 2 leavepieces detailed further below:
    - DYS-UK-003430 – relevant excerpts from Dysport adult spasticity dosing leave piece and DYS-UK-003502 accompanying briefing document
    - DYS-UK-003328 – relevant excerpts from Dysport adult cervical dystonia dosing leave piece and DYS-UK-003501 accompanying briefing document.
- 2 clinical slide decks containing information on time to retreatment as follows:

- Relevant exerts from DYS-UK-003421 – clinical review of upper and lower limb data for use by KAMs & DYS-UK-003422 – clinical review of cervical dystonia data for use by KAMs and accompanying briefing documents.

Whilst other representative materials were in circulation between these dates, these did not contain any claims in relation to duration of effect and were not provided due to them being out of scope of the current complaint.

Materials with duration of effect

Ipsen provided excerpts of certified representative materials, as well as where appropriate, the accompanying respective briefing documents, which contained references to Dysport duration of effect claims. These materials were approved and circulated subsequent to the close of the inter-company dialogue on 16 December 2018.

Ipsen had reviewed its materials which included the following statements around duration of effect:

- 'Dysport - a toxin with a long-lasting effect' found in two leavepieces
- Time to retreatment statements in the clinical slide decks.

The data used to substantiate these statements were provided.

Dysport – a toxin with a long-lasting effect

Ipsen submitted that this claim was substantiated by data on file (DYS-UK-003437), which contained data on re-treatment intervals for the clinical indications of adult upper limb, adult lower limb and adult cervical dystonia pertaining to the Dysport UK label SPC as well as analysis of pivotal clinical study data on the respective clinical indications. See below:

Dysport is indicated for symptomatic treatment of focal spasticity of Upper Limb in adults

DYSPORT SPC - Section 4.2

Clinical improvement may be expected one week after injection and may last up to 20 weeks. Injections may be repeated every 12 - 16 weeks or as required to maintain response, but not more frequently than every 12 weeks. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of Dysport and muscles to be injected.

Gracies JM *et al* 2017 was an open-label extension of the pivotal study (Gracies JM, *et al* 2015), which evaluated the effect of aboboutlinumtoxinA (500U and 1000U) over repeated treatment cycles in hemiparetic patients. Data evaluating 1st injection administered (500U or 1000U) after the double blind study showed that 36.8% of patients (56/152) did not require re-injection before week 16 (this was also based on study protocol where patients were assessed if an injection at week 12 was required).

Dysport was indicated for symptomatic treatment of focal spasticity of lower limb in adults affecting the ankle joint due to stroke and traumatic brain injury

Dysport SPC – Section 4.2

Repeat Dysport treatment should be administered every 12 to 16 weeks, or longer as necessary, based on return of clinical symptoms but no sooner than 12 weeks after the previous injection.

Gracies JM *et al* 2017 was an open-label extension of the pivotal study (Gracies JM, *et al*) which evaluated the effect of aboboutlinumtoxinA (1000U and 1500U) over repeated treatment cycles in adult patients post-stroke or traumatic brain injury. Data evaluating 1st injection (1000U and 1500U) administered after the double blind study showed that 20.1% of patients (45/230) did not require re-injection before week 16 (this was also based on study protocol where patients were assessed if an injection at week 12 was required).

Dysport was indicated in adults for symptomatic treatment of spasmodic torticollis (cervical dystonia)

Dysport SPC - Section 4.2

The relief of symptoms of torticollis might be expected within a week after the injection. Injections might be repeated approximately every 16 weeks or as required to maintain a response, but not more frequently than every 12 weeks.

Truong D *et al* 2005 *was* a multicentre, double-blind, randomized, controlled trial which assessed the safety and efficacy of Dysport in cervical dystonia patients in the USA. A total of 88 patients were randomly assigned to receive one treatment with Dysport (500 units) or placebo. Participants were followed up for 4 to 20 weeks, until they needed further treatment. They were assessed at baseline and weeks 2, 4, 8, 12, 16, and 20 after treatment. The following analysis was concluded from the paper: **In treating Cervical Dystonia the average duration of response to Dysport was 22.8 weeks** in those that achieved a response in a double-blind, randomised, placebo-controlled study. The duration of the response was defined as the number of weeks between treatment and the recurrence of symptoms, as defined by a return of the TWSTRS-Total score to within 10% of baseline.

This claim was intended for the appropriate target audience, ie healthcare professionals in clinical specialist fields such as neurorehabilitation (to treat adult spasticity) and neurology (adult cervical dystonia), where these health professionals would be well versed with the clinical management and experienced with the various treatment options (including toxins such as Dysport). In the context of understanding the mechanism of action of botulinum toxin treatment, in particular with botulinum toxin type A (BoNT-A), duration of effect was an important consideration for health professionals. Not only would this help health professionals understand the clinical properties and its utility in practice, but guidance and education on time to next injection (ie re-treatment) was crucial to help health professionals in patient management in between injections, hence important from both efficacy and safety perspective.

The therapeutic use of botulinum toxin for was first licensed nearly 30 years ago (Dysport was licensed for therapeutic use in 1989). The clinical use of botulinum toxin for patient treatment in neurorehabilitation, neurology and paediatric cerebral palsy was widely known by health professionals in these therapy areas and who therefore were not unfamiliar with its pharmacodynamic and pharmacokinetic properties.

A review publication by *Kukreja R and Singh BR* (2015) stated:

> 'therapeutic utility of botulinum toxin lies in its ability to specifically and potently inhibit involuntary muscle activity for an **extended duration……** The duration of effect lasts somewhere between 3 months and 6 months'.

A medical reference 'Clinical Uses of Botulinum Toxins' authored by 2 key international clinical experts, in collaboration with an international clinical expert contributors, noted that:

> 'one of the many attractive features of type A BoNT for therapeutic applications is its **prolonged duration** (3-12 months in humans depending on the condition treated) of efficacy.'

Ipsen submitted, therefore, that it was well versed in clinical literature and from health professionals that duration of action of BoNT-A was widely known and understood by the clinical community where BoNT-A was used therapeutically.

Other medicines used for the treatment of spasticity and other movement disorders might include oral agents such as baclofen and benzodiazepines (such as diazepam); dosing for these medications were required daily (in the case of baclofen, up to 3 times a day). Therefore, in relation to a description 'long lasting effect' of a toxin for therapeutic use, this was consistent with the clinical understanding by UK health professionals on the effects after treatment for patients, where injection interval was no less than 12 weeks for adult spasticity and cervical dystonia within the Dysport UK licence.

In the field of neurosciences, treatment considerations were very diverse as it could be used in various clinical indications. There were not many new interventions and the use of BoNT-A for therapeutic use was well-established from clinical, literature and scientific platforms. Health professionals would therefore be able to contextualise the data correctly and Ipsen was not making any claims to imply that Dysport had any special merit over other medicines.

Dysport time to retreatment – Clinical slides decks

DYS-UK-003421 – Clinical slide Deck 'Use of Dysport for Adult Spasticity'

In the clinical slide deck (DYS-UK-003421) slides were included which were taken from studies investigating the time to retreatment of abobotulinumtoxinA (Dysport) in adult patients with (i) Upper limb spasticity (ULS) and (ii) Lower limb spasticity (LLS), post stroke or traumatic brain injury. Gracies JM *et al* 2017 was an open-label extension of the pivotal study (Gracies JM *et al* 2015;) which evaluated the effect of aboboutlinumtoxinA (500U and 1000U) over repeated treatment cycles in hemiparetic patients. Data evaluating 1st injection administered (500U or 1000U) after the DB study showed that 36.8% of patients (56/152) did not require re-injection before week 16 (this was also based on study protocol where patients were assessed if an injection at week 12 was required).

With respect to ULS the clinical slide deck shows results from figure 2A of the poster outlining the retreatment times at cycle 1 with a statement in the material **'36.8% were not injected before week 16'**.

Gracies JM *et al* 2017 was an open-label extension of the pivotal study (Gracies JM, *et al* 2017) which evaluated the effect of aboboutlinumtoxinA (1000U and 1500U) over repeated treatment cycles in adult patients post-stroke or traumatic brain injury. Data evaluating 1st injection (1000U and 1500U) administered after the DB study showed that 20.1% of patients (45/230) did not require re-injection at before week 16 (this was also based on study protocol where patients were assessed if an injection at week 12 was required).

With respect to LLS the clinical slide deck showed results from figure 2A of the poster outlining the retreatment times at cycle 1 with a statement in the material outlining **'20.1% were not injected before week 16'**.

As outlined previously, this data presented was consistent with Section 4.2 of the Dysport SPC:

> *'Dysport SPC - Section 4.2*
>
> Focal Spasticity in adults: Upper limb
>
> Injections may be repeated every 12 - 16 weeks or as required to maintain response, but not more frequently than every 12 weeks. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of Dysport and muscles to be injected
>
> Focal Spasticity in adults: Lower limb
>
> Repeat Dysport treatment should be administered every 12 to 16 weeks, or longer as necessary, based on return of clinical symptoms but no sooner than 12 weeks after the previous injection.'

DYS-UK-003422 – Clinical slide Deck 'Use of Dysport for Spasmodic Torticollis (Cervical Dystonia)'

Ipsen stated that the clinical slide deck (DYS-UK-003422) included slides which were taken from study published by Troung D *et al* 2005 investigating the efficacy and safety of botulinum type A toxin (Dysport) in cervical dystonia. This was a multicentre, double-blind, randomized, controlled trial assessing the safety and efficacy of Dysport in cervical dystonia patients in the USA. A total of 88 patients were randomly assigned to receive one treatment with Dysport (500 units) or placebo. Participants were followed up for 4 to 20 weeks, until they needed further treatment. They were assessed at baseline and weeks 2, 4, 8, 12, 16, and 20 after treatment.

This concluded that: **In treating Cervical Dystonia the mean duration of response to Dysport was 22.8 weeks with a standard deviation (± SD) of 12.5,** in those that achieved a response in a double-blind, randomised, placebo-controlled study. The duration of the response was defined as the number of weeks between treatment and the recurrence of symptoms, as defined by a return of the TWSTRS-Total score to within 10% of baseline.

The clinical slide deck (DYS-UK-003422) included:

> 'A greater proportion of patients treated with Dysport 500U achieved a therapeutic response vs. placebo-treated patients (14 of 37 patients (38%) vs. 7 of 43 (16%)), while the mean (±SD) duration of response (number of weeks between treatment and the

> recurrence of symptoms, as defined by a return of the TWSTRS-Total score to within 10% of baseline) to Dysport was 22.8 weeks (12.5).'

Ipsen submitted that as outlined previously, this data was consistent with Section 4.2 of the Dysport SPC.

Dysport SPC – Section 4.2: Spasmodic torticollis posology

> 'Injections may be repeated approximately every 16 weeks or as required to maintain a response, but not more frequently than every 12 weeks.'

Post-inter-company dialogue promotion

Merz alleged that reports of continued breaches of the commitments Ipsen made under inter-company dialogue had come from across the country, with a specific example being attributed to a named senior hospital pharmacist. Ipsen asked to be provided with a copy of the complaint so that it could verify when the alleged discussion took place. From its records, it ascertained that a meeting took place between two commercial Ipsen employees and the named senior hospital pharmacist in March 2019.

The Ipsen employees present at that meeting were aware of the inter-company dialogue with Merz and had also received the internal briefing DYS-UK-003026 and so were familiar with the requirements of this briefing in terms of the promotion of Dysport. The allegations attributed by Merz to the senior hospital pharmacist as to the matters discussed were not consistent with the requirements set out in the Ipsen internal briefing. The employees present at the meeting recalled that the topics discussed at that meeting related to pricing issues and commercial terms. Ipsen stated its investigation into this matter had not revealed any evidence to support the allegations attributed by Merz to the senior hospital pharmacist.

Although Ipsen did not have details of any specific allegations made by Merz against Ipsen at either of the other two named hospitals, for completeness Ipsen had carried out a search of its records to ascertain whether any discussions had taken place regarding 'sustained duration of effect' and had been unable to locate any evidence as to this allegation.

Summary

In summary, Ipsen rejected Merz's allegations that it had acted in breach of agreed commitments resulting from the inter-company dialogue. As highlighted above, Ipsen submitted that it promptly and thoroughly actioned all of the agreed outcomes from the inter-company dialogue and had not used the same or similar claims since this time, whilst at all times being clear with Merz that it would continue to promote Dysport within licence.

Ipsen could not locate any evidence which supported the allegations attributed to the named senior hospital pharmacist, nor any records relating to interactions at other centres which evidences a strategy of differentiation around sustained duration of effect. Further, it was inappropriate for Merz to base its complaint on an unsubstantiated allegation by a single healthcare professional, particularly as the precise wording of what was said must, to a degree, be uncertain.

Finally, Ipsen submitted that claims and statements used in certified representative materials in circulation concerning duration of effect were:

- properly substantiated;
- consistent with the information in the Dysport SPC relating to time to retreatment, therefore within Dysport UK licence;
- in relation to 'long lasting effect' of a toxin for therapeutic use, consistent with the clinical understanding by UK health professionals on the effects after treatment for patients, where injection interval was no less than 12 weeks for adult spasticity and cervical dystonia within the Dysport UK licence;
- intended for the appropriate target audience, ie health professionals in clinical specialist fields such as neurorehabilitation (to treat adult spasticity) and neurology (adult cervical dystonia), where these health professionals would be well versed with the clinical management and experienced with the various treatment options (including Dysport), hence would be able to contextualise the data correctly; and
- did not fall outside the actions agreed with Merz as part of the inter-company dialogue as promotion within licence was always reserved to Ipsen.

Ipsen therefore, strongly refuted any suggestion that it acted in breach of Clauses 7.2, 7.3, 7.10 nor Clause 9.1 of the Code.

PANEL RULING

The Panel noted Ipsen's submissions regarding the SPC for Dysport and intervals between treatments which varied according to the indication. Dysport was not to be used more frequently than every 12 weeks, some indications were for use at 12-16 weeks or longer, another was approximately every 16 weeks or as required to maintain a response. For focal spasticity of upper limb clinical improvement might last up to 20 weeks.

Health professionals would assess when further treatment was needed. It was of course acceptable for companies to promote their medicines in line with the particulars in the SPC.

The data provided by Merz and Ipsen compared Dysport with placebo in various indications. No data was submitted by either Merz or Ipsen comparing the efficacy of the various toxins. It appeared that there were no comparative data.

The Panel noted that the claims 'Dysport extends time to retreatment in some patients' and 'Dysport offers sustained effect of treatment up to 24 weeks in some patients for upper and lower limb spasticity' were the subject of inter-company dialogue and that Ipsen confirmed that materials with these claims would be withdrawn. Ipsen submitted that it reserved the right to present clinical data within licence covered in the Dysport SPC.

Merz referred to activities in three different geographical areas following the closure of inter-company dialogue. Little detail had been provided. Ipsen acknowledged there had been a meeting with one pharmacist in one geographical area where employees discussed pricing issues and commercial terms. Ipsen submitted that the employees present were aware of the inter-company dialogue with Merz and had received briefing material DYS-UK-003026. The Panel noted that this briefing material did not refer to the inter-company dialogue but did state in bold, 'When discussing Dysport, it is important no comparison should be made with other toxins as we do not have any prospective head to head studies'. In relation to the two other

geographical areas, Ipsen submitted that it had no evidence that any discussions had taken place regarding 'sustained duration of effect' as alleged.

The Panel considered that there was little evidence provided by Merz that representatives' conversations demonstrated that Ipsen promoted 'differentiation on a platform of sustained duration of effect' and in particular that Dysport had a longer duration of effect than Xeomin as alleged. The Panel considered that given the material which had been withdrawn as a result of inter-company dialogue it was not unreasonable that some employees might consider that the previous claims that Dysport extended time to retreatment and offered sustained effect of treatment was a reason for choosing Dysport in preference to other toxins. Further the representatives had not been told in the withdrawal briefing document that materials with these claims had been withdrawn following inter-company dialogue. Representatives were told that the material was withdrawn in readiness for a prescribing information update.

Ipsen provided some pages from its current materials and the associated representative briefing documents. Time to retreatment with Dysport from the open-label extension phase of studies in adults with upper limb and lower limb spasticity featured in materials. The associated briefing documents stated, 'No direct comparisons should be made to other toxins in the absence of head to head studies'. There was no complaint about Ipsen's new material. The claims that Ipsen agreed to withdraw following inter-company dialogue with Merz, as stated above, were not within the pages of the current materials provided by Ipsen.

The Panel considered that Merz had not shown on the balance of probabilities that Ipsen employees had promoted at the three named hospitals that Dysport had a longer duration of effect than other toxins or that it promoted differentiation on a platform of sustained duration of effect as alleged. It therefore ruled no breach of Clauses 7.2, 7.3 and 7.10 as alleged. Nor was there evidence that Ipsen had not maintained high standards. Therefore, the Panel ruled no breach of Clause 9.1 of the Code.

APPEAL BY MERZ

Merz Pharma appealed the Panel's rulings of no breaches of Clauses 7.2, 7.3, 7.10 and 9.1.

Merz alleged that Ipsen in its promotion of Dysport had continued (after the conclusion of apparently successful inter-company dialogue in 2018) to promote messages that created an unsubstantiated and misleading impression of superior duration of effect of Dysport (relative to competitor toxins) to UK health professionals.

BACKGROUND

During October-December 2018 Merz and Ipsen were engaged in inter-company dialogue as a result of a complaint by Merz about Ipsen's use of claims for the duration of clinical effect of its product Dysport. The essence of the complaint was that the claims 'Dysport offers sustained effect of treatment up to 24 weeks in some patients for upper and lower limb spasticity' and 'Dysport extends time to retreatment in some patients' (found in the leavepiece Why Choose Dysport)) were not capable of substantiation and were misleading. Merz alleged breaches of Clauses 7.2, 7.3, 7.10 and consequently of 9.1.

Merz stated that inter-company dialogue concluded with Ipsen's agreement to withdraw a series of printed materials and made the following undertakings (emphasis added by Merz):

1 The immediate withdrawal of all items with duration of effect claim highlighted, **or similar claims**, including: leavepieces, economic models, slide sets, electronic sales aids or items in any format including promotional and non-promotional materials.

2 The immediate withdrawal of all items with the claim 'Think beyond a 12-week injection' highlighted, **or similar claims**, including: leavepieces, economic models, slide sets, electronic sales aids or items in any format including promotional and non-promotional materials.

3 To ensure that no further items with the following claims remained in circulation:

'Dysport offers sustained effect of treatment up to 24 weeks in some patients for upper and lower limb spasticity'

'Dysport extends time to retreatment in some patients.'

4 To ensure that all licensed indications are sufficiently prominent in any replacement materials.

5 To reinforce to the Dysport sales and MSL team that all activities must be in accordance with the Code and that, in the absence of comparative studies, no cross-trial comparisons could be made.

Merz stated that Ipsen had reserved the right to present Dysport clinical data within the licence covered in the Dysport SPC. Ipsen also sent out an internal briefing (DYS-UK-003026) on the withdrawal of materials dated 1 November 2018. By 16 December 2018 Merz was satisfied and the inter-company dialogue drew to a close.

Merz alleged that after the conclusion of the inter-company dialogue the company became aware of continued promotional activity claiming a longer duration of effect for Dysport versus Xeomin and after investigation made a complaint directly to the PMCPA. The core of Merz's arguments followed.

Merz alleged that it was worth exploring some of the additional detail not covered by Ipsen in its response to the Panel in helping the Appeal Board to understand the validity of the clinical data on which Ipsen sought to find its claims.

Merz alleged that in its response Ipsen had emphasised heavily the contents of the SPC for Dysport. To better understand the validity of the claims in the context of Clause 7 of the Code it was important to understand the clinical protocols for the pivotal studies involved along with some background into the disease states being treated and any protection that a regulatory document conferred to a pharmaceutical company under the Code.

Dysport clinical trial protocols

Merz alleged that in defending the claim 'Dysport - a toxin with a long duration of effect', and other claims, Ipsen had cited the post hoc analysis Gracies *et al* Duration of effect of abobotulinum toxinA (Dysport) in adult patients with upper limb spasticity (ULS) post stroke or

traumatic brain injury, Toxins Madrid January 2017, without making reference to the pivotal study on which the publication was based, namely Safety and efficacy of abobotulinumtoxinA for hemiparesis in adults with upper limb spasticity after stroke or traumatic brain injury: a double blind randomised controlled trial. Gracies, *et al* 2015.

Merz alleged that the two key aspects of the pivotal study, upon which the post hoc analysis was based, were the primary efficacy variable and the protocol for reinjection.

Merz noted firstly, the primary efficacy variable in the pivotal study was mean change in modified Ashworth score at week 4 which was chosen to ensure consistency with previous studies. The primary efficacy variable was met at week 4, however no significant difference was presented for this variable versus placebo for weeks 12, 16 and 20. Similarly, in the presentation of the results for this primary efficacy variable in Dysport promotional materials, P values were given for week 4 but not provided for weeks 12, 16 and 20. Given the very significant overlap of the error bars it could be assumed the there was no significant difference between Dysport and placebo for the primary measure of efficacy in this pivotal study beyond week 4. Consequently, and at the very least, caution should be applied to general claims of sustained duration of effect for weeks 12, 16 and 20 for this study population, whether referencing this study or any post hoc analysis based on the data generated by the study.

Merz noted secondarily, the investigators were given fixed timepoints to offer reinjection to the patient population. The reinjection intervals were 12, 16 or 20 weeks following the previous injection. It should be highlighted that should a patient not receive an injection at week 12, for whatever reason, there was no opportunity to inject before the next fixed injection point at week 16. Should a patient not be injected at week 12 it was therefore unknown if they would have benefited from reinjection at week 13, 14 or 15 for example. Accordingly, the statement ‘did not require re-injection before week 16’ from the Ipsen response was, in itself, clearly incapable of substantiation and was misleading. Whilst the claim was present in the SPC it remained unevidenced, and, in the absence of evidence the SPC represented an inappropriate source for substantiation.

Disease background and botulinum neurotoxin

Merz stated that the licensed indication of focal spasticity was a neuromuscular condition which could be successfully treated by botulinum neurotoxin (BoNT) which acted to chemically denervate the muscles (thereby relaxing them). The rate at which BoNT ‘wears off’ was considered to be combination of (a) a neurophysiological consequence of the body creating new nerve endings to compensate for the ones lost through the irreversible chemical denervation caused by BoNT and (b) dependent upon the dose of BoNT used and the accuracy of the injecting health professional’s technique.

Merz noted that all three widely commercially available BoNTs (Xeomin, Botox and Dysport) used the same (Hall strain) bacterial source of Clostridium botulinum in the commercial product. Xeomin was purified 150kD toxin and Dysport and Botox both contained complexing proteins which dissociate on injection to leave the 150kD BoNT which then caused the chemical denervation. Merz alleged that because of this common bacterial source there would be no expectation of any difference in duration of effect between the toxins, nor were there (after thirty years of clinical use) any robust comparative studies which showed any significant difference in the duration of effect. With this in mind, any claims which sought to create the impression that Dysport had special merit in terms of duration of effect compared to other brands could be

misleading (either directly or by implication or through undue emphasis) to health professional's (Clauses 7.2 and 7.3) thereby potentially claiming special merit that might lead to the irrational use of the product (Clause 7.10).

Regulators and the Code

Merz noted that whilst the regulators (MHRA) were a diligent and thorough body their raison d'etre was patient safety and not Code compliance. Merz alleged that there were numerous incidences of the MHRA approving materials through the pre-vetting protocol which were subsequently found in breach of the Code. Ipsen's assertion that they would 'reserve the right to present Dysport clinical data within the licence covered in the Dysport Summary of Product Characteristics' was insufficient to substantiate promotional claims. Merz stated the fact that Ipsen had used such an approach AND drawn conclusions which could not be evidenced by published data called into question their understanding of the Code and Ipsen's culture of compliance.

Against this background Merz moved on to events that occurred since the closure of the 2018 inter-company dialogue.

Merz alleged that despite a successful inter-company dialogue reports from customers of a continuance of the duration of effect campaign were maintained. Whilst disappointing it was not altogether unsurprising given this activity would bring Ipsen UK in line with what was clearly a global campaign, with similar claims still reflected in global corporate materials and symposia today. Merz stated that its interpretation of Ipsen's continued activity was in direct breach of undertakings 1, 2 and 5 of Ipsen's written response to Merz (30 November 2018). It was the repeated alleged breach of the same behaviour that prompted Merz, under Paragraph 5.3 of the Constitution and Procedure, to report the alleged breaches direct to the Panel. This complaint was made to the PMCPA on 24 July 2019 and became the basis for Case AUTH/3228/7/19 (current case).

Merz noted the Panel's ruling that, on the balance of probabilities, Merz was unable to provide sufficient evidence to support the allegation that Ipsen sales staff employed the use of the duration claims at three UK hospitals as outlined in its complaint letter. Merz alleged the contrary and directed the Appeal Board to the following points:

1 Ipsen committed to make widespread changes to its promotional materials as a result of the 2018 inter-company dialogue and to remove all printed materials carrying the specific claims at issue, committed to not reproduce those (or similar) claims and would direct its field-based teams to act at all times within the Code. This approach was not consistent with the action of a company which genuinely believed its claims were justifiable.

2 That Ipsen claimed it withdrew the materials simply to make way for a new campaign that was due in 'early 2019' was simply not plausible. Sales teams represented the single biggest cost for a pharmaceutical company and to commit to remove core promotional materials for a period of at least two months (the introduction date in early 2019 of the new materials was unknown but they were withdrawn on 24 October) defied business logic.

3 To initiate a promotional material withdrawal was a significant act that required diligence, resources and importantly a reason. It was incomprehensible that the campaign materials were withdrawn as a result of the inter-company dialogue but that no reason was provided to the sales and MSL teams other than a forthcoming prescribing information change (note that a prescribing information change would only require material withdrawal ONCE the new prescribing information and materials were printed). Merz alleged that it did not have sight of the internal briefing on the withdrawal of materials (DYS-UK- 003026) dated 1 November 2018 but to take such a dramatic step without providing the customer-facing part of the business with a reason was difficult to imagine. At the very least this would prompt questions from the sales team as to why but additionally the failure to highlight a potential compliance breach or risk would in itself compound the chance of a Code breach being repeated. Indeed, the Panel identified that 'it was not unreasonable that some employees might consider that the previous claims that Dysport extended time to retreatment and offered sustained effect was a reason for choosing Dysport in preference to other toxins. Further the representatives had not been told in the withdrawal briefing document that materials with these claims had been withdrawn following intercompany dialogue. Representatives were told that the material was withdrawn in readiness for a prescribing information update'

4 In Ipsen's response it stated that it had reviewed its materials approved and circulated subsequent to the close of the inter-company dialogue on 16 December 2018 and these included the following statement around duration of effect: 'Dysport - a toxin with a long-lasting effect'. Merz alleged that this statement was a hanging comparison, inviting customers to draw the conclusion that Dysport had a long lasting effect when compared to other botulinum toxin formulations.

The fact that Ipsen had confirmed to the Panel that it continued to use such a statement was in direct contravention of the spirit of the undertaking given in inter-company dialogue.

5 Ipsen's references to other spasticity medications with daily dosing schedules (eg baclofen and diazepam) as a defence for using 'long lasting effect' to describe Dysport was incongruous. The health professionals who used BoNT were exclusively secondary care specialists in the UK. They were experts in their field and to suggest that using the phrase long-lasting was helpful in allowing them to understand the difference between oral baclofen and IM BoNT was patronising and obfuscating. Further the phrase 'Dysport - A toxin with a long-lasting effect' clearly drew a comparison to other botulinum toxins. Just as the unused claim 'Dysport - A medicine with a long-lasting effect' would have clearly drawn comparison to alternative medicines, such as baclofen and diazepam.

6 A written statement from an independent named health professional, a senior hospital pharmacist, confirmed these activities and specifically that the activities and messages were supported by at least one senior sales staff member who, in their response, Ipsen stated was aware of the undertaking: The statement confirmed:

> 'Whilst together you mentioned the recent discussion with Ipsen regarding Dysport and Xeomin. During the meeting with Ipsen, which was led by a senior Ipsen employee, it was argued that the Trust was disadvantaging the

patients in its care by using an inferior product, Xeomin, rather than Dysport which it was further argued had a longer duration of effect. The consequence of this practice meant that patients were missing out on the superior product and the Trust was running unnecessary clinics, and consequently wasting resource. You were offered promotional material, referencing claims from a US study, supporting these arguments which you declined to see as you believed the claims to be misleading, in light of the Trust's direct experience in previously switching from Dysport to Xeomin. During our meeting you expressed concern that these messages could have a destabilising effect on the local health economy providing an unnecessary distraction for an otherwise already busy service.11 'I can confirm that you have summarised by interaction with Ipsen accurately.'

7 Ipsen submitted that it had investigated the call to the senior hospital pharmacist and confirmed that one took place in March 2019. Merz alleged that Ipsen referred to the 'allegations attributed to [the senior hospital pharmacist]' but failed to understand that these were not allegations attributed by Merz to the senior hospital pharmacist but made by him/her directly about a promotional call that Ipsen had confirmed took place. The above was a verbatim email from the pharmacist. Ipsen, in its investigation claimed that the two employees recalled 'to the best of their recollection, the topics discussed at that meeting related to pricing issues and commercial terms. Merz stated that it would strongly contest that the written statement from the senior hospital pharmacist was entirely consistent with a discussion that related to a longer duration of effect which would reduce reinjection frequency and therefore save the trust money. Ipsen's investigation had been cursory and there had been no robust substantiating documents (emails or CRM screenshots) that refuted Merz's allegation and the senior hospital pharmacist's recollection of the meeting.

8 Ipsen had sought to use the SPC as a shield to the requirements of the Code and in claiming patients in the pivotal studies 'did not require re-injection before week 16' without any means of substantiation had shown poor comprehension and/or respect for the Code. That such a senior person in a compliance role made such an assertion must also call into question the compliance culture at Ipsen.

Merz alleged that in the light of the fact Ipsen failed to brief the sales team the claims at issue were subject to an inter-company undertaking at the time of withdrawal, that materially similar claims were still in use throughout the Dysport promotional material, that these claims were demonstrably part of the wider corporate strategy for product differentiation, that Ipsen had a misguided belief that unevidenced claims could be shielded by careful wording of the SPC, and finally that a senior UK health professional had gone on record that these claims continued to be made, Merz alleged that, on the balance of probabilities, Ipsen had continued to promote Dysport through an unevidenced duration of effect claim relative to other BoNTs and in doing so had breached Clauses 7.2, 7.3 and 7.10 of the Code. Given these actions across the business and at such a senior level, coupled with the breach of prior inter-company dialogue undertaking, Merz also alleged this collectively represented a clear breach of Clause 9.1.

…..…..*…..*…..*

Following referral to an independent referee, Merz was provided with redacted enclosures to Ipsen's response to the complaint. Merz subsequently provided supplementary comments to its above appeal.

…..…..*…..*…..*

Withdrawal of materials following inter-company dialogue

Merz noted that the internal briefing (DYS-UK-003026) highlighting the withdrawal of promotional material in readiness for a prescribing information update had now been shared. Merz stated that in its appeal it had already been argued that in the case of a prescribing information update there was generally no requirement to withdraw materials until the revised materials were available. Having reviewed the withdrawal notification in full, Merz alleged that in failing to highlight the inter-company dialogue, which preceded the withdrawal, and include clear guidance for the sales team to discontinue the use of the disputed claims, or similar claims, Ipsen was in clear breach of the spirit of the inter-company dialogue and, by association, the Code. Merz stated that this lack of commitment to follow through on the obligation to brief sales staff tipped the balance of probabilities in favour of continued use of the claims, as reported by the the senior hospital pharmacist who provided a statement that the claims continued to be made. The fact that the pharmacist stated the meeting included a senior member of the Ipsen management team, who Ipsen confirmed was aware of the undertaking, reinforced the lack of commitment to accept the inter-company dialogue as binding.

Sales force briefing documents

Merz stated that DYS-UK-003502 and DYS-UK-003501 represented the Ipsen briefing documents for some of the revised promotional materials following the withdrawal. Within each of the documents there were 4 bolded headings. The third heading, 'Dysport – A toxin with a long-lasting effect', gave a clear steer on the purpose of the new materials, namely to differentiate Dysport within the BoNT-A market as a BoNT-A with a long-lasting effect. This claim, in itself, had already been discussed in the Merz appeal but would be revised given the additional insights offered within the briefing notes.

Merz stated that a toxin with a long-lasting effect represented a clear comparison to alternative BoNT-A preparations. Much in the same way as a claim of 'A toxin with a low price' would lead the reader to believe Dysport was competitively priced when compared to other BoNT-A preparations. Given the inter-company dialogue commitment to refrain from duration of effect claims incapable of substantiation it was surprising to see the prominence of the comparative statement in the briefing material. The reason for its prominence was captured below with the bullet: 'This was an important claim to be comfortable with substantiating in call as it is a key message in a lot of messaging around Dysport'.

Merz alleged that this statement implied that there had been some discomfort with the substantiation of the claim within the sales team, it also clearly highlighted the message 'Dysport - a toxin with long-lasting effect' was central to the Ipsen UK commercial strategy. It was the only message reinforced within the new material, which in Merz's view, was completely aligned with an Ipsen global corporate campaign which set out to directly compare the duration of effect of Dysport to that of Xeomin and Botox. Further, given there had been recent and clear undertakings directly relating to claims regarding duration of effect, it was extraordinary that no effort was made to highlight these recent undertakings around the now sensitive duration of

effect claims, especially given its absence in the previously cited materials withdrawal briefing (DYS-UK-003026).

Spasticity claims and substantiation

Merz alleged that in DYS-UK-003502, no comparative evidence was offered to support the claim of 'Dysport – A toxin with a long-lasting effect'. The substantiation relied on general wording within the SPC and the often cited, non-peer-reviewed, post hoc analyses by Gracies *et al*, which was presented as a poster at toxins in 2017. The claim, 'over 35% of patients did not require re-treatment before week 16' was misleading and in breach of Clause 7.2 of the Code. If the patients within the study did not meet the protocol for re-injection at week 12, the next opportunity for re-injection would be week 16. The statement capable of substantiation should read; 'Over 35% of patients did not require re-injection at week 12'. This was a statement of fact, the former was a statement of conjecture and was incapable of substantiation.

Merz alleged the fact that over 35% of patients were not injected at week 12 was not in the least surprising. Bensmail *et al,* which was known to Ipsen, conducted a survey of physicians and patients attending botulinum toxin clinics for the treatment of spasticity in Europe and the US. Within the survey it was identified that 32.9% of injections were routinely given in weeks 13-14, a fact which underlined the misdirection of the Ipsen claim.

Dystonia claims and substantiation

Merz alleged that a similar emphasis was again placed on the central importance of the claim 'Dysport – A toxin with a long-lasting effect' in the staff briefing for DYS-UK-003501 'Cervical Dystonia Dosing Guide'. Once again, the fact that the claim was 'important' and a 'key message in a lot of the brand messaging around Dysport' was made.

Merz alleged that the first substantiation of the claim made reference to the SPC. The second substantiation made reference to the Truong 2005 study, specifically that 'the average duration of response to Dysport was 22.8 weeks in those that achieved a response in a double blind, randomised, placebo controlled study'. This substantiation was misleading by omission. Within the study only patients that were 'responders' proceeded beyond week 4. The study Author noted that 38% of patients were withdrawn from the Dysport arm of the study at week 4 due to non-response and were not represented in the mean 22.8% duration of response claim. Of those patients who demonstrated a response to Dysport at week 4 only 41% of patients remained within the study by week 12. The author also highlighted the wide variation in reported duration of response (9-46 weeks) with the influence of the majority (shorter responders) reducing the median duration of response to 18.5 weeks.

Merz alleged that Ipsen had consciously chosen therefore to use a subset analysis rather than an intent to treat protocol. This cherry-picking approach to clinical data had long been recognised as inappropriate in the promotion of medicines. The direction of the sales team to substantiate the 'Dysport – A toxin with a long-lasting effect' claim with the evidence that Dysport had a duration of effect of 22.8 weeks in Dystonia without clearly stating the limitations of the data represented a failure to maintain high standards and a breach of Clause 9.1 and a failure to provide adequate training of representatives and a breach of Clause 15.1 of the Code [It should be noted that a breach of Clause 15.1 was not made in the original submission and consequently would fall outside of the appeal, however it was stated for completeness]. Further

to this, these data clearly in no way substantiated the underlying comparative claim implied, that Dysport had a long-lasting effect when compared to alternative formulations of BoNT-A.

Merz alleged that, in summary, the additional enclosures provided by Ipsen in its submission and shared with Merz further supported the central argument that:

1 The sales staff, who had been previously supplied with materials containing duration of effect messages incapable of substantiation were not briefed the messages were subject to inter-company dialogue, withdrawn and not appropriate for further dissemination.
2 Differentiation on a platform of duration of effect remains 'important' and central to the Ipsen strategy and continued to feature across 'a lot of brand messaging around Dysport' placing the company at very high risk of breaching its inter-company dialogue undertaking.
3 The claim 'Dysport – A toxin with a long-lasting effect' was incapable of substantiation as no comparative data was available.
4 Ipsen's defence of the claim, which it was argued represented a general statement in relation to all anti-spasmodic therapies, was disingenuous given the central nature of the claim acknowledged in the staff briefing material.
5 The claim was supported by two misleading data on file references, Gracies which was misleading by design and Truong, which was misleading by omission.
6 These actions resulted in poorly trained sales staff entirely likely to breach the previous inter-company dialogue and were encouraged by a senior staff member in a call reported on.

Merz alleged that taking these additional insights, and given the written testimony of the senior hospital pharmacist in a meeting that was undisputed to have taken place, it was most certainly now beyond the balance of probabilities that comparative and disparaging statements were made implying a superior duration of effect for Dysport when compared to Xeomin. Taken collectively the repeated misrepresentation of data and the failure to effectively brief the sales team to make them 'comfortable with substantiating these claims' represents a failure in the most basic standards expected of a pharmaceutical company.

COMMENTS FROM IPSEN

Ipsen submitted that it maintained its position as previously articulated on the matters raised in Merz's appeal letter and strongly denied the allegations that Ipsen had continued to promote Dysport messages that were unsubstantiated and misleading (and that by doing so, Ipsen was in breach of the spirit of the 2018 inter-company dialogue).

Promotion of Dysport on the basis of its duration of effect

Ipsen submitted that it had undertaken extensive and prolonged efforts to act within the agreements of the inter-company dialogue with Merz which commenced in October 2018. Ipsen stated that it had continued to promote Dysport within the boundaries of the marketing authorisation, making no comparisons to other products with no misleading claims; this had been stated to the Ipsen sales team and reiterated in briefing materials. The Panel concurred with this in its determination of the case in December 2019.

Ipsen submitted that contrary to Merz's allegation, it had not promoted its product on a platform of 'longer duration of effect' or 'sustained duration'. Rather a statement of fact had been employed: 'A toxin with a long-lasting effect' made no comparison with any other product and was therefore not a hanging comparison, direct or indirect. It was a stand-alone statement referring to Dysport's long duration of action. The statement is supported by the SPC which outlines the various retreatment times that could be achieved for different indications, which varied between indications, and repeat injection was no more frequently than every 12 weeks. For the avoidance of any doubt, data on file summarising this statement and with supporting data were certified by Ipsen in June 2019; this had been supplied previously (DYS-UK-003437). This factual statement was capable of substantiation with no direct or implied comparison. The statement was consistent with the clinical understanding of UK health professionals on the effects after treatment for patients, where injection interval was no less than 12 weeks for adult spasticity and cervical dystonia within the Dysport UK licence. Extensive explanation of this statement was provided to the Panel and it ruled no breaches of the Code. Again, this had been explained and reiterated to the sales team to ensure they understood the boundaries of this claim for each indication and importantly that their briefing included the statement 'No direct comparisons should be made to other toxins in the absence of head to head studies' which could clearly be seen in the briefing material for both leavepieces (DYS-UK- 003502 and DYS-UK-003501).

Ipsen submitted that in its criticism of 'Dysport - A Toxin with a long-lasting effect' Merz had attempted to disparage the robustness of both the SPC, as well as the cited data. What Merz had overlooked was that the SPC was a compilation of Phase I-III data which underwent periodic and required updates to ensure that the available body of evidence was captured in a succinct document; it was a collection of data from many studies, not just one trial. A study that Merz specifically criticized was a study by Gracies *et al* which was a phase III, international, multicentre, double blind randomised single cycle study of Dysport in adults with upper limb spasticity and was followed by a long-term open label extension. The open label study patients received up to 4 additional treatment cycles over a max of 1 year. At each treatment cycle retreatment was per investigators clinical judgement and possible at weeks 12, 16, 20 and 24. As a reflection of clinical practice, patients usually were given retreatment dates, it was possible they might experience symptom return before their retreatment date but it was not usual that they could then return to the health professional for re-treatment as and when they felt. This was similarly reflected in this study design, as it was not possible to track all patients and have them drop in between weeks 12 and 16 as they felt their symptoms were returning. At retreatment cycle 1:

- 63.2% of patients were retreated at week 12
- 17.1% at week 16
- 9.9% at week 20
- 9.9% at week 24 or later.

Ipsen submitted that in short, many did require re-treatment in this study at week 12, but a substantial proportion did not until weeks 16, 20 or 24. It was unclear why Merz had quoted another study (Bensmail *et al*) given that this study was not part of the original complaint, appendices or materials.

Ipsen submitted that Merz had further attempted to criticise the data supporting 'Dysport - A toxin with a long-lasting effect' in the use of the Truong publication. It was unfortunate that Merz's allegations regarding the results were incorrect. Merz stated that '38% of patients were

withdrawn at week 4 due to non-response'; this was incorrect at 100% were participating at 4 weeks. At week 8, 59% of Dysport treated patients remained in the study, versus 35% in the placebo group. By week 12, 41% of Dysport treated patients with 21% of placebo patients remaining. The 41% remained in the study beyond 12 weeks whilst the placebo group reduced to 14%. Ipsen had been precise and explicit in the nature of the results, stating in both the Data on File (DYS-UK-003437) and the KAM briefing (DYS-UK-003501), 'In treating Cervical Dystonia the average duration of response to Dysport was 22.8 weeks in those that achieved a response in a double-blind, randomised, placebo-controlled study. The duration of the response was defined as the number of weeks between treatment and the recurrence of symptoms, as defined by a return of the TWSTRS-Total score to within 10% of baseline'. These results were taken from those presented in the peer-reviewed publication; it was inappropriate for Merz to suggest that Ipsen should re-analyse the published data and present alternative figures.

Ipsen submitted that it was deeply concerned by Merz's repeated assertion that Ipsen as the marketing authorization holder was not permitted to promote Dysport within the boundaries of the SPC, and that the studies which supported the Dysport licence were questionable from a Regulatory perspective. Ipsen took its responsibility as a marketing authorization holder very seriously and ensured that it participates fully and willingly in the continuous benefit-risk assessment of its products through all mandated pharmacovigilance activities. Accordingly, Ipsen undertook responsible and balanced promotion of its pharmaceuticals. If Merz considered that the Dysport marketing authorization was in question, this should be a matter for the Competent Authority, the MHRA. The Panel had previously accepted that Ipsen was permitted to present clinical data within licence covered in the Dysport SPC.

Ipsen submitted that it had gone to great lengths to employ data throughout the Dysport marketing materials which were a mixture of pivotal and post marketing data, all of which were entirely consistent with the SPC, with a balance of efficacy and safety information.

Ipsen submitted that it would firstly like to challenge Merz's assertion that the email from the senior hospital pharmacist constituted the written testament of the pharmacist. At best, this was Merz's interpretation of a conversation that it was not party to, which it had then attempted to attribute to the senior hospital pharmacist. It was not his/her direct testimony. As mentioned previously, Ipsen did not have any contemporaneous record of the exact conversation that took place between the senior hospital pharmacist and Ipsen in March 2019. Ipsen stated that it had shared the email with the two employees concerned, and with the caveat that this conversation took place over 14 months ago, and had asked them to again attempt to recall the conversation in the light of Merz's allegation. Ipsen stated that it remained satisfied that there was no evidence that this conversation was in any way disparaging to Merz nor to any other competitor. Both employees confirmed that the conversation was focused around the senior hospital pharmacist's rationale for using or not using Dysport. There was some pricing/tender discussion and some discussion on what data/local data the pharmacist would wish to see in support of the Dysport value proposition (which was perhaps where reference was made to the American Academy of Neurology review referred to in Ipsen's promotional materials which it assumed was the US study referred to in the email). Ipsen stated that it had not been able to locate any evidence to support Merz's claims in its submission. Ipsen stated that it should also mention that at no point had the senior hospital pharmacist complained to Ipsen about the meeting in March 2019, nor mentioned it further to Ipsen. Ipsen continued to enjoy a very positive working relationship with the senior hospital pharmacist across its entire product portfolio.

Closing comments

Ipsen stated that in summary, it continued to strongly reject the allegations that it had acted in breach of Clauses 7.2, 7.3, 7.10 and 9.1 and it maintained its position that:

- Ipsen sales staff had been appropriately briefed regarding duration of effect messages and the withdrawal of materials
- The duration of effect statements employed were copied from the SPC and were fully substantiated
- The claim 'Dysport - a toxin with a long-lasting effect' was not a comparative claim, had been fully substantiated and had been accepted previously by the Panel
- The statement was consistent with the clinical understanding by UK health professionals on the effects after treatment for patients, where injection interval was no less than 12 weeks for adult spasticity and cervical dystonia within the Dysport UK license
- The supporting data was from phase III and IV studies which were accurately captured in both the SPC and marketing materials
- Ipsen staff were comprehensively trained and carefully briefed on each claim used in marketing materials.

Ipsen stated that it had demonstrated throughout its response and through the materials it had submitted previously that it did not agree with the points made in the appeal letter. Ipsen stated that it had addressed the main points and explained how it had not behaved contrary in letter or spirit to any clauses of the Code, and therefore Ipsen asserted that it had maintained high standards in accordance with Clause 9.

FINAL COMMENTS FROM MERZ

Merz noted that Ipsen had highlighted an error in its appeal regarding the point that the study author noted that 38% of patients were withdrawn from the Dysport arm of the study at week 4 due to non-response. Merz agreed that this observation was correct in that slightly more Dysport patients withdrew from the study at the 4-week timepoint than the 38% claimed, this was highlighted in the verbatim extract from the paper 'Substantially more placebo patients (27 of 43, 63%) than Dysport patients (15 of 37, 41%) ended their participation at week 4'. The Author went on to report, when discussing duration of effect, that only 38% of Dysport patients met the criteria for a therapeutic response, and subsequently that for those who responded to Dysport the mean duration of the response of 22.8 weeks. In analysing the paper, Merz understood that the 22.8 week duration of response was a subgroup of the intention to treat cohort. Merz restated that to present the 22.8 week duration of response without very clearly acknowledging the data referred only to a responder subgroup was misleading.

Merz noted Ipsen's submission that in making the claim 'Dysport – A toxin with a long-lasting effect' no comparison was drawn to any other product. This position was restated in Ipsen's response. Merz would not restate its opposition to this position, only that it was highly unlikely that a class effect relating to duration of action would be described as 'an important claim to be comfortable with substantiating in call as it was a key message in a lot of messaging around Dysport' throughout representative briefing material.

Merz alleged that Ipsen repeatedly made the case that it was asserting a marketing authorisation holder was not permitted to promote its product within the boundaries of the

product SPC. To be clear Merz was not arguing that Ipsen could not market Dysport within the boundaries of the Dysport SPC, purely that the SPC did not, in of itself, represent a substantiation of a product claim.

APPEAL BOARD RULING

The Appeal Board noted that the claims 'Dysport extends time to retreatment in some patients' and 'Dysport offers sustained effect of treatment up to 24 weeks in some patients for upper and lower limb spasticity' were the subject of inter-company dialogue and that Ipsen confirmed that materials with these claims had been withdrawn.

The Appeal Board noted that Ipsen had not referred to the inter-company dialogue in the briefing material for sales representatives to indicate why the material was being withdrawn. The Appeal Board considered that this would have reinforced to representatives that such claims should no longer be used in line with Ipsen's inter-company agreement.

The Appeal Board noted that Merz had referred to activities in three different geographical areas following the closure of inter-company dialogue. The only evidence provided was the email exchange between Merz and the named senior hospital pharmacist (dated March 2019) which referred to a meeting between Ipsen and the pharmacist held in March 2019. The Appeal Board noted the nature of the evidence in that Merz had provided its written account of the interaction between Ipsen and the senior hospital pharmacist based on the pharmacist's account as described to Merz. It was not directly from the pharmacist. The account written by Merz, referred to Ipsen representatives stating that '…the Trust was disadvantaging the patients in its care by using an inferior product, Xeomin, rather than Dysport which it was further argued had a longer duration of effect…'. Whilst noting that the account was not written by the senior hospital pharmacist , the Appeal Board noted when provided with Merz's account, the senior hospital pharmacist had replied to Merz and agreed that Merz had summarised his/her account of his interaction with Ipsen accurately. The Appeal Board noted that Ipsen had no detailed call notes from the meeting with the senior hospital pharmacist. However, in its submission Ipsen stated that when interviewed by Ipsen the representatives who met with the senior hospital pharmacist were adamant that the account was not correct. The Appeal Board was surprised that Ipsen had not contacted the pharmacist directly about the matter. The representatives from Ipsen at the appeal stated that this was due to sensitivity as it was unsure if the senior hospital pharmacist knew his/her email was being used by Merz to submit a complaint to the PMCPA rather than merely to resolve the matter directly with Ipsen as stated in the communication between Merz and the senior hospital pharmacist . The Appeal Board considered that it was unusual for a senior hospital pharmacist to be involved with a dispute between two pharmaceutical companies.

The Appeal Board noted that the current Ipsen advertising campaign included the claim 'Dysport – A toxin with a long-lasting effect'. The Appeal Board noted Ipsen's submission that the claim was a statement of fact in that all neurotoxins had a long-lasting effect – including Dysport and that the representative's briefing document stated 'When discussing Dysport, it is important no comparison should be made with other toxins as we do not have any prospective head to head studies'. The representatives from Ipsen at the appeal stated that the purpose of the claim was to address the unmet need of patients whose conditions would benefit from a neurotoxin where oral therapies had failed. The Appeal Board noted that the promotional material made no mention of this and there was little explanation provided in the promotional material or the briefing material to explain what was meant by the '…long-lasting effect' and the strength of any

supporting data. The purpose of many promotional claims was to differentiate one medicine from another. Whilst the claim might be factual, in the context of a main promotional claim, the Appeal Board considered it would be read in relation to other medicines and was misleading in relation to the undue emphasis on the duration of effect of Dysport with regard to other neurotoxins. The Appeal Board noted that there had been no head to head studies to show a difference in the duration of effect of any neurotoxins. The Appeal Board also considered that the email from Merz and the senior hospital pharmacist provided evidence that Ipsen representatives had, on the balance of probabilities, been misleading with regard to the implied benefit of Dysport in terms of its duration of effect. The Appeal Board consequently ruled a breach of Clause 7.2. The appeal on this point was successful. In this regard the Appeal Board did not consider that it had evidence that the implied benefit of Dysport in terms of its duration of effect amounted to a misleading comparison with Xeomin as alleged and the Appeal Board consequently ruled no breach of Clause 7.3. The appeal on this point was unsuccessful.

The Appeal Board noted its comments above concerning the senior hospital pharmacist's confirmation of Merz's account of his/her meeting with Ipsen employees, Ipsen's failure to inform its representatives regarding its inter-company dialogue with Merz and the claim within the current Dysport promotional material. The Appeal Board considered that, on the evidence provided, the Ipsen representatives had not encouraged the rational use of Dysport and the implied benefit with regards to its duration of effect could not be substantiated and it therefore ruled a breach of Clause 7.10. The appeal on this point was successful.

The Appeal Board considered that, overall, Ipsen had failed to maintain high standards and ruled a breach of Clause 9.1. The appeal on this point was successful.

Complaint received **25 July 2019**

Case completed **7 October 2020**