CASE AUTH/2289/12/09

MERCK SHARP & DOHME v ALCON

Azarga leavepiece

Merck Sharp & Dohme alleged that a leavepiece which promoted the comfort of Azarga (brinzolamide/timolol eye drops) issued by Alcon Laboratories was not consistent with the summary of product characteristics (SPC) and that the claims made were not supported by clinical evidence. In particular the claim 'Significantly more comfortable than Cosopt' was exaggerated and did not reflect the evidence and the over-emphasis of 'comfort' or 'comfortable', by the inclusion of 13 claims for this in just 8 pages of material, was exaggerated, all-embracing and misleading.

Merck Sharp & Dohme submitted that the data comparing the ocular discomfort of Azarga and Cosopt was not consistent with a general claim that Azarga was 'Significantly more comfortable than Cosopt Solution'. By failing to note in the leavepiece that the cited studies (Vold *et al* 2008; Mundorf *et al* 2008) had measured transient post-instillation discomfort, Alcon misleadingly implied that the discomfort experienced might be longer-lasting and therefore more clinically significant.

Merck Sharp & Dohme stated that the over-emphasis of one aspect of the comparative tolerability, comfort, did not fairly reflect all the evidence. For example the comparisons of comfort between Azarga and Cosopt did not refer to blurred vision which was a common adverse event for Azarga. The Azarga SPC also listed eye irritation and eye pain as common side effects. This was not consistent with describing Azarga as comfortable.

In Vold *et al* patients in both treatment groups (Azarga and Cosopt) reported statistically significant increases in discomfort scores after switching from prior monotherapy to study medicine, and a significant number of patients experienced discomfort on drop instillation with Azarga. The increase in discomfort score for Azarga compared with previous treatment was +0.49, p=0.0028; after 1 week 51% of Azarga patients experienced some discomfort.

There was no definition in the leavepiece of what was meant by comfort. Two studies were described which used different scales and criteria for measuring ocular discomfort but this was also not made clear. Since comfort was not a well-used and understood concept in ophthalmology it appeared all-embracing and misleading when used repeatedly without explanation.

The detailed response from Alcon Laboratories is given below.

The Panel noted that the front page of the leavepiece was headed 'Find comfort in our strength' and featured the claim 'New Azarga Suspension brings you the strength you would expect, with the comfort your patients deserve'. The product logo in the bottom right-hand corner included the strapline 'Where strength meets comfort'. Page 3 of the leavepiece was headed '… and the comfort they desire' and featured a bar chart using data reported in Vold *et al*. The bar chart was headed 'Patients Reported Greater Discomfort with Cosopt than with Azarga Suspension'. A claim above the bar chart read 'Significantly more comfortable than Cosopt Solution'. The bar chart plotted mean ocular discomfort score on a scale from 0 (no discomfort) to 4 (very severe discomfort); at week 1 the mean ocular discomfort score for Azarga (n=48) was 0.77 (1 = mild discomfort) and that for Cosopt (n=47) was 1.53 (2 = moderate discomfort). This difference was statistically significant (p=0.0003). Vold *et al* reported that the distribution of the ocular discomfort scores at week 1 for Azarga was: 0 (no discomfort), 48.9%; 1 (mild discomfort), 34%; 2 (moderate discomfort), 10.6%; 3 (severe discomfort), 4.3% and 4 (very severe discomfort), 2.1%. The comparable distribution of scores for Cosopt was: 0, 14.9%; 1, 38.3%; 2, 27.7%; 3, 17% and 4, 2.1%. The Panel thus considered that although there was a greater likelihood of feeling discomfort following the instillation of Cosopt vs Azarga, 34% of Azarga patients nonetheless reported mild discomfort with Azarga and 17% reported moderate to very severe discomfort. The comparable scores for Cosopt were 14.9% and 46.8%.

The Panel considered that the repeated references to comfort in the leavepiece might be seen as implying that there was no discomfort at all with Azarga which was not so for 24 out of the 47 patients evaluated; one of those patients reported very severe discomfort. The Panel noted that the Azarga SPC stated that eye pain, eye irritation and foreign body sensation in the eyes were common adverse reactions. Ocular discomfort as defined by Vold et al was any of the following: burning, stinging, a feeling heat or warmth, sharp pain or smarting pain. Foreign body sensation was not included in the definition.

The Panel considered that the claim 'Significantly more comfortable than Cosopt Solution' was exaggerated as alleged and did not reflect the evidence and had not been substantiated. Vold

***et al* had evaluated the ocular discomfort of Azarga and Cosopt and the claim should reflect this. Breaches of the Code were ruled. Upon appeal by Alcon, the Appeal Board considered that the claim was not inconsistent with Vold *et al* or the Azarga SPC. The claim headed a bar chart which provided the relevant data from Vold *et al*. The Appeal Board did not consider that the claim was misleading or exaggerated; it was capable of substantiation and no breach was ruled.**

The Panel considered that the repeated use of comfort/comfortable was exaggerated, all embracing and misleading as alleged. A breach of the Code was ruled which was upheld on appeal by Alcon.

The Panel did not consider that the failure to note that Vold *et al* and Mundorf *et al* measured transient post-instillation discomfort misleadingly implied that the discomfort might be longer lasting and therefore more clinically significant as alleged. No breach of the Code was ruled.

The Panel noted that 'comfort' was not defined in the leavepiece. The two studies cited in support of comfort claims (Vold *et al* and Mundorf *et al*) had, in fact, assessed discomfort. As noted above, Vold *et al* had defined discomfort and asked patients to evaluate any such discomfort on a scale of 0 to 4. Mundorf *et al* had not described what was meant by discomfort but had asked patients to complete an ocular discomfort scale (0 (no discomfort) to 9 (substantial discomfort)) approximately one minute after treatment and to complete a preference question. Although noting its ruling above regarding the use of the word 'comfort', the Panel nonetheless considered that it was misleading as alleged not to define the term. The Panel considered that the leavepiece was misleading and exaggerated as alleged. A breach of the Code was ruled. Upon appeal by Alcon, the Appeal Board noted that the intended audience would understand what comfort meant for their glaucoma patients; Alcon had provided comments from ophthalmologists to support its submission. The Appeal Board considered that it was not misleading as alleged not to define 'comfort' in the leavepiece. The Appeal Board considered that the leavepiece was not misleading or exaggerated in this regard. No breach of the Code was ruled.

With regard to blurred vision, the Panel noted that it was a common side-effect with both Azarga and Cosopt. Although inconvenient for the patient, the Panel did not consider that blurred vision was a discomfort factor. In the context of a discussion about the relative discomfort of Azarga and Cosopt, the Panel did not consider that it was misleading not to refer to blurred vision as alleged. No breach of the Code was ruled.

Merck Sharp & Dohme Limited complained about an eight page, A5 leavepiece (ref AZG:SJ:12/08:LHC) for Azarga (brinzolamide/timolol eye drops) issued by Alcon Laboratories (UK) Limited. Azarga was indicated for the decrease of intraocular pressure (IOP) in adult patients with open-angle glaucoma (OAG) or ocular hypertension for whom monotherapy provided insufficient IOP reduction. Merck Sharp & Dohme marketed Cosopt, a dorzolamide/timolol combination with a similar indication. Dorzolamide and brinzolamide were carbonic anhydrase II inhibitors; timolol was a non-selective ß-adrenergic blocker.

COMPLAINT

Merck Sharp & Dohme alleged that the leavepiece, entitled 'Find comfort in our strength', was not consistent with the Azarga summary of product characteristics (SPC) and that the claims made were not supported by clinical evidence. Specifically:

- the claim 'Significantly more comfortable than Cosopt' was exaggerated and did not reflect the evidence and
- the over-emphasis of 'comfort' or 'comfortable', by the inclusion of 13 claims for this in just eight pages of material, was not consistent with the SPC and constituted an exaggerated, all-embracing and misleading claim.

Merck Sharp & Dohme submitted that there was data comparing the ocular discomfort and drop instillation of Azarga and Cosopt which was not consistent with a general claim that Azarga was 'Significantly more comfortable than Cosopt Solution'. The discomfort experienced by patients following instillation of eye drops was transient, lasting a few seconds. The results from the studies referenced in the Azarga leavepiece were based on questions asked immediately after instillation, one of them referred to a period of one minute (Vold *et al* 2008; Mundorf *et al* 2008). Alcon's promotion failed to make clear that the effects referred to were short-lived. By failing to point out that both these studies had measured transient post-instillation discomfort, Alcon misleadingly implied that the discomfort experienced might be longer-lasting and therefore more clinically significant.

Merck Sharp & Dohme stated that there was also an over-emphasis in promotion of one aspect of the comparative tolerability of the two products – comfort as defined by Alcon – which did not fairly reflect all the evidence such that a recipient could form their own opinion of the therapeutic value of the medicine. For example the comparisons of comfort between Azarga and Cosopt did not refer to blurred vision which was a common adverse event for Azarga on drop instillation that could be very distressing for patients. The Azarga SPC also listed eye irritation and eye pain as common side effects. This was not consistent with describing Azarga as comfortable.

In Vold *et al* patients in both treatment groups (Azarga and Cosopt) reported statistically significant increases in discomfort scores after switching from prior monotherapy to study medicine, and a

significant number of patients experienced discomfort on drop instillation with Azarga. The increase in discomfort score for Azarga compared with previous treatment was +0.49, p=0.0028; after 1 week 51% of Azarga patients experienced some discomfort.

There was no definition in the leavepiece of what was meant by comfort. Two studies were described which used different scales and criteria for measuring ocular discomfort but this was also not made clear. Since comfort was not a well-used and understood concept in ophthalmology it appeared all-embracing and misleading when used repeatedly without explanation.

Merck Sharp & Dohme alleged that the Azarga leavepiece was in breach of Clauses 7.2, 7.4 and 7.10.

RESPONSE

Alcon explained that open angle glaucoma (OAG) was a chronic, progressive condition with characteristic changes to the optic disc which, if left untreated, would lead to irreversible blindness. In most OAG patients, lowering of (IOP) (initially with eye drops in most cases) was the only treatment that delayed or halted the progression of the disease. Patients who did not show the characteristic changes to the optic disc, but nevertheless had a higher than normal IOP (ocular hypertension), might also be given similar treatment, as a protective measure.

As OAG was a progressive condition, it required long-term medical treatment which produced little discernible benefit for the patient, since they would not notice any improvement in their vision. For this reason, and because administration of eye drops could be difficult and unpleasant, compliance with therapy might be poor. Failure to comply adequately with treatment would result in an uncontrolled IOP and further loss of vision. One way to encourage good compliance was to reduce the number of eye drops used and so combination therapies, such as Azarga and Cosopt, had been introduced and were becoming increasingly popular.

The pH of tears was close to neutral (pH 7), and although the eye could tolerate a range of pH values around the normal physiological level, the general aim was to produce eye drops with a pH value as close to neutral as possible, in order to provide maximal compatibility with the ocular environment.

Cosopt was introduced first as a slightly acidic solution (pH around 5.6), and as a consequence of the results obtained in clinical trials, the SPC listed burning and stinging as very common side effects. In order to reduce the potential for similar levels of ocular irritation Azarga was formulated as a suspension with a pH of 7.2 and, based on the results from clinical studies, the SPC listed irritation and pain only as common ocular side effects. The Azarga SPC also stated that ocular discomfort upon instillation was significantly lower than for Cosopt. The relatively poor ocular comfort of Cosopt had been confirmed in specifically designed comfort studies and in comparative clinical studies against Azarga and other glaucoma products.

The claim in the leavepiece 'Significantly more comfortable than Cosopt' was the conclusion of a parallel group, randomised ocular comfort clinical study in patients with OAG or ocular hypertension (n=96), (Vold *et al*). Discomfort (defined as feelings of burning, stinging, a feeling of heat or warmth, sharp pain or smarting pain) was assessed on a 5-point scale at baseline for the current glaucoma medicine and then after one week of treatment with either Cosopt or Azarga. Significantly more patients in the Cosopt group reported mild, moderate, or severe ocular discomfort and significantly more patients in the Azarga group reported no ocular discomfort.

Similarly Mundorf *et al*, in a prospective, double-blind, randomized, single-dose, crossover patient preference study involving 127 subjects with ocular hypertension or OAG, reported that mean discomfort scores were significantly lower for Azarga than for Cosopt and that significantly more patients reported eye irritation and eye pain as adverse events after instillation of Cosopt . Manni *et al* (2008), in a one-year, randomized, double-blind, active-controlled, parallel group trial involving 437 patients with OAG or ocular hypertension who required a change in therapy, reported a significantly higher incidence of adverse drug reactions in the Cosopt group primarily due to the higher incidence of ocular irritation (burning) and ocular pain (stinging).

Further, the legitimacy of Alcon's claims must be judged in light of relevant contextual factors. There were currently only two topical fixed dose combination products containing a carbonic anhydrase inhibitor, Azarga and Cosopt. Since Cosopt was launched first and was now well established and familiar to the Azarga leavepiece target audience, it was natural that claims for Azarga should focus on comparative efficacy and safety against Cosopt. Comparative clinical studies, submitted in support of the Azarga marketing authorization application demonstrated no significant difference in efficacy between the products, but a difference in safety, represented by a significantly higher level of reports of eye irritation (ie discomfort) with Cosopt. No significant difference was found in the incidence of other side effects, including blurred vision. As a result, ocular comfort of the two products was directly compared by Vold *et al* and in a patient preference study (Mundorf *et al*). Based on the clinical data and the approved SPC for Azarga, it could therefore be correctly claimed that Azarga was as effective as Cosopt (strength) and exhibited less discomfort (ie was more comfortable). Alcon noted that 'comfort' was only mentioned six times in the leavepiece, without a link to efficacy (strength) also being

made. Alcon did not consider that this was excessive given that comfort was the main differentiator between Azarga and Cosopt.

The leavepiece included claims about efficacy, convenience and comfort. Since comfort was the only significant difference found in clinical studies between Azarga and Cosopt it was reasonable and appropriate that this property was specified by Alcon in communications with ophthalmologists, even if this might be inconvenient to Merck Sharp & Dohme.

Merck Sharp & Dohme's assertion that, 'two studies were described which used different scales and criteria for measuring ocular discomfort but this was also not made clear', was irrelevant considering that the two studies were consistent in using a similar numerical discomfort scale to measure comfort and the patient experience in the two studies clearly was similar – Vold *et al* defined ocular discomfort as any of the following: burning, stinging, a feeling of heat or warmth, sharp pain or smarting pain; Mundorf *et al* reported ocular irritation (burning) and ocular pain (stinging) much more frequently as adverse events with treatment. Alcon submitted that blurred vision was irrelevant to the claims made in the leavepiece as this was not generally considered to be a comfort/discomfort factor (as explained by reference to the statements of eminent practising UK ophthalmologists discussed below). Indeed, in the literature relating to the instillation of eye drops, comfort/discomfort was generally related to subjective symptoms such as burning, stinging and irritation. Blurred vision was not a typical or even common component of any definition of a measure of comfort or discomfort. This was illustrated by references which provided a summary of some recent relevant published papers relating to the treatment of OAG and ocular hypertension (ie the field of expertise of the target recipients of the leavepiece in question).

Further, Mundorf *et al* reported blurred vision separately as an adverse event and distinguished it from discomfort factors. This was an appropriate distinction to make because although more patients experienced blurred vision with Azarga compared with Cosopt, most still preferred Azarga, 'suggesting that the blurred vision occurring with [Azarga] was less annoying than the ocular discomfort experienced with [Cosopt]'. Thus, although Merck Sharp & Dohme evidently found it inconvenient that Azarga had a better comfort profile compared with Cosopt, this was no basis for alleging that the comparison Alcon drew between the two products was unsubstantiated, misleading or not of clinical relevance.

Alcon provided correspondence from ophthalmologists who were highly experienced in treating patients with OAG/ocular hypertension; Alcon noted that they viewed blurred vision and comfort as two distinct issues:

Alcon considered that the information, claims and comparisons regarding the comfort of Azarga complied with the Code, in particular because they were:

> based on an up-to-date evaluation of all the evidence, reflected that evidence clearly and were not misleading (in accordance with Clause 7.2);
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> the material was sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of Azarga (in accordance with Clause 7.2);
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> the information, claims and comparisons were substantiated (in accordance with Clause 7.4); and
>
> the claims made were not exaggerated or all-embracing (in accordance with Clause 7.10).

Alcon's compliance with the Code was demonstrated in the discussion below, which addressed the comfort claims in the context of the fundamental issue at stake, namely whether comparative studies measuring 'discomfort' were indicative of a product's 'comfort' profile. Alcon was firmly of the view that they were, based on:

> the use of the words 'comfort' and 'discomfort' and their inter-changeability (ie less discomfort equated to more comfort) in literature relating to ophthalmic products;
>
> ophthalmologists' understanding of the terms;
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> the nature of the products in question; and
>
> as a matter of natural language.

Alcon submitted that contrary to Merck Sharp & Dohme's disingenuous assertion that comfort was 'not a well-used and understood concept in ophthalmology', the comfort of anti-glaucoma eye drops had frequently been studied. Typically, comfort would be assessed by the measurement or reporting of symptoms of discomfort as in Vold *et al* and Mundorf *et al*. Further, it might be seen from the relevant publications that less discomfort and more comfort were essentially interchangeable concepts. For example, although Mundorf *et al* measured discomfort factors, the authors clearly considered these factors to be indicative of the products' comfort profile:

> 'In the present study, significantly more patients reported blurred vision after instilling [Azarga] compared with [Cosopt]. Despite these observations, most patients in this study still preferred [Azarga], suggesting that the blurred vision occurring with [Azarga] was less annoying than the **ocular discomfort** experienced with [Cosopt].
>
> One important reason for their preference was **ocular comfort**. The patients in our study

reported significantly **lower ocular discomfort** scores after instilling [Cosopt] compared to [Azarga] … **Ocular comfort** is a quality that glaucoma patients desire in an IOP-lowering medication' (emphasis added).

Similarly, in Vold *et al*, comfort and discomfort were both used as shown in the following three example extracts; the publication clearly considered discomfort factors to be indicative of the products' comfort profile (which was why the study was entitled 'A One-Week **Comfort** Study …': (emphasis added)

'The results of this clinical trial demonstrate that the **ocular comfort** of [Azarga] ophthalmic suspension dosed twice-daily **is superior** to that of [Cosopt] dosed twice-daily in patients with open-angle glaucoma or ocular hypertension'.

'Several studies have suggested that **greater comfort** can have a positive effect on patient adherence to IOP-lowering medications'.

'In summary, patients with open-angle glaucoma or ocular hypertension reported **less discomfort** with [Azarga] ophthalmic suspension than with [Cosopt] ophthalmic solution' (emphasis added).

The above example extracts clearly illustrated that comparative studies measuring discomfort factors were indicative of the products' comfort profile. In support of its position Alcon cited publications where greater comfort and less discomfort were interchangeable. Accordingly, the use of the word comfort was not all-embracing in breach of Clause 7.10, or misleading (by exaggeration or otherwise) in breach of Clause 7.2 as alleged. Further, since comfort was the only significant difference found in clinical studies between Azarga and Cosopt, it was reasonable and appropriate that Alcon referred to this property in its communications with ophthalmologists; however, Alcon refuted the suggestion that comfort was over-emphasised.

Alcon submitted that comfort and comfortable were well understood clinical terms used frequently ophthalmologists in their everyday clinical practice including with their OAG/ocular hypertensive patients (to ensure they understood why they had to adhere to therapy). Indeed, at an Alcon advisory panel meeting, the six eminent practising UK ophthalmologists commented that Merck Sharp & Dohme's claims (ie that the data did not support Alcon's claim that Azarga was significantly more comfortable than Cosopt; the word comfort was not well-understood in ophthalmology; and blurring of vision should be reported as an aspect of the comfort of Azarga rather than as a side effect) were not sustainable.

Alcon referred to correspondence from ophthalmologists, experienced in treating patients with OAP/ocular hypertension, which supported its position that the target audience would understand the concept of comfort and comfortable and that the terms, as applied to eye drops for the treatment of patients with OAG or ocular hypertension, were to an extent relative rather than absolute.

Alcon submitted that, the fact that, in Vold *et al*, there was an increase in mean discomfort score when patients were switched from their previous IOP-lowering monotherapy to the fixed combination (brinzolamide/timolol or dorzolamide/timolol) did not mean that the term comfort could not be applied to Azarga, as argued. The comparison drawn was between the respective comfort profiles of the two fixed combination products, compared to one another. It was clear in Vold *et al* that there was a lower increase in mean discomfort score in patients switched to Azarga than in those switched to Cosopt.

Further, although the Azarga SPC listed eye pain and eye irritation (which would both be described as discomfort factors) as common side effects, it was nevertheless legitimate to compare the relative comfort of Azarga and Cosopt. Indeed, the Cosopt SPC listed burning and stinging (which would also be described as discomfort factors) as very common side effects. This distinction was borne out by Vold et al and Mundorf et al which demonstrated greater comfort/less discomfort with Azarga compared with Cosopt; the Azarga SPC which stated that 'in three controlled clinical trials, the ocular discomfort upon instillation of Azarga was significantly lower than that of [Cosopt] and the Azarga European Public Assessment Report (EPAR) which reported that 'The ocular discomfort adverse event related reactions in [pivotal safety and efficacy studies] support the claim of better tolerability of Azarga as compared to Cosopt' and that '… the applicant has justified the claim of overall better tolerability for Azarga compared to Cosopt'.

As acknowledged by Merck Sharp & Dohme there was data which specifically compared ocular discomfort on drop instillation with Azarga and Cosopt. However, according to Merck Sharp & Dohme, such data were not indicative of the comfort profile of Azarga vs Cosopt: 'this [ie, the comparative data] **was not consistent** with a general claim that Azarga was significantly more comfortable than Cosopt' (emphasis added). However, Merck Sharp & Dohme offered no satisfactory explanation as to why it considered that less discomfort upon instillation was inconsistent with more comfort. Indeed, in an apparent attempt to support its assertion that less discomfort was inconsistent with more comfort, Merck Sharp & Dohme stated: 'The discomfort experienced by patients following instillation of eye drops was transient …. By failing to point out that both these studies [Vold *et al* and Mundorf *et al*] had measured transient post-instillation discomfort, Alcon misleadingly implied that the discomfort experienced might be longer-lasting and therefore more clinically significant'.

However, the above statement was totally irrelevant to Merck Sharp & Dohme's point; the fact that the discomfort was temporary did not contradict or undermine the legitimacy of the claim that Azarga was 'Significantly more comfortable than Cosopt', the relevant point being whether the comparative studies measuring discomfort factors were indicative of the products' comfort profile (such that the greater discomfort associated with Cosopt might be translated as the greater comfort associated with Azarga), which they clearly were. The claim did not imply that discomfort was long-lasting or of greater clinical significance than it actually was: indeed, notwithstanding the fact that the discomfort was temporary, Mundorf *et al* stated that 'Patients with ocular hypertension or open-angle glaucoma preferred [Azarga] over [Cosopt]. This is likely due to the greater ocular discomfort associated with [Cosopt]'.

Further, it was evident that greater discomfort – albeit temporary upon instillation – might have a negative effect on patient compliance. Mundorf *et al* stated that: '… it is not unreasonable to believe that patients may take a medication less frequently than prescribed if it is associated with significant side effects, including ocular discomfort'. Similarly, Vold *et al* stated that: 'Several studies have suggested that greater comfort can have a positive effect on patient adherence to IOP-lowering medications'.

Finally, as a matter of natural language it was clear that comfort and discomfort were two sides of the same coin and that more comfortable was synonymous with less uncomfortable (or less discomfort) (in other words, a question of perspective: glass half empty/glass half full was the same thing). In this case, experts in the field used the terminology interchangeably. Alcon provided a comment from a consultant ophthalmologist to support its position in this regard.

Based on the above, Alcon firmly considered that comparative studies measuring discomfort factors were indicative of a product's comfort profile, such that the greater discomfort associated with Cosopt might be translated as the greater comfort associated with Azarga. In this context Alcon noted that in assessing a product's comfort profile, it was logical to measure factors of discomfort rather than comfort, as discomfort was associated with definable signals (such as burning, stinging and pain), the fewer of which there were, the greater the comfort. Further, the means of assessing comfort/discomfort had now been approved by three ethics committees, assessed by the European Medicines Evaluation Agency on two different occasions during two different licence applications and presented in three different peer-reviewed articles, which was further evidence of the robustness of the comparative data for Azarga vs Cosopt and the legitimacy of assessing comfort by reference to factors of discomfort. Therefore, it was natural that the studies under discussion measured factors of discomfort rather than factors of comfort and it did not mean that Alcon should be limited to referring to discomfort instead of comfort.

Accordingly, Alcon believed that the Azarga leavepiece complied with the Code.

The claims and comparisons were based on an up-to-date evaluation of all the evidence. The claim, 'Significantly more comfortable than Cosopt' was based on Vold *et al*. Mundorf *et al* and Manni *et al* provided further support for the comfort claims. The claims and comparisons reflected that evidence clearly because comparative clinical studies measuring discomfort factors were indicative of a product's comfort profile. They did not mislead by exaggeration or otherwise. It was acceptable to make comfort claims in relation to Azarga considering that comfort and comfortable were well-used and understood concepts in ophthalmology which ophthalmologists used in their everyday practice including with glaucoma patients. Further, ophthalmologists understood that the terms comfort and comfortable, as applied to eye drops for the treatment of OAG or ocular hypertension, were to an extent relative rather than absolute; comfort was not claimed in absolute terms. The leavepiece was consistent with the Azarga SPC and EPAR.

Alcon further submitted that the leavepiece was sufficiently complete to enable recipients to form their own opinion of the therapeutic value of Azarga. The leavepiece was directed at ophthalmic specialists who were familiar with 'comfort' terminology as applied to eye drops for the treatment of OAG/ocular hypertension and would appreciate that comfort was typically defined by measuring/reporting factors of discomfort. Alcon thus denied a breach of Clause 7.2.

Alcon denied a breach of Clause 7.4. The claims and comparisons were capable of substantiation and had been substantiated. Reference was made in particular to Vold *et al*, Mundorf *et al* and Manni *et al*. Clinical studies measuring 'discomfort' factors were indicative of a product's comfort profile.

Alcon submitted that the claims made in the leavepiece were not exaggerated because they were consistent with the Azarga SPC and EPAR. Further, the claims were supported by robust scientific evidence; clinical studies measuring discomfort factors were indicative of a product's comfort profile. The terms comfort and comfortable were not over-emphasised in the leavepiece: since comfort was the only significant difference found in clinical studies between Azarga and Cosopt, it was reasonable that Alcon should emphasis this property in its communications with ophthalmologists.

The claims made in the leavepiece were not all-embracing because comfort terminology had a specific application in the ophthalmic field and was well-understood by the specialists to whom the leavepiece was directed. Alcon denied a breach of Clause 7.10.

In light of all the arguments raised above, and given the familiarity ophthalmologists had with the concept of comfort in the context of glaucoma medicines, Alcon denied breaches of Clauses 7.2, 7.4 and 7.10.

PANEL RULING

The Panel noted that the front page of the leavepiece was headed 'Find comfort in our strength' and featured the claim 'New Azarga Suspension brings you the strength you would expect, with the comfort your patients deserve'. The product logo in the bottom right-hand corner included the strapline 'Where strength meets comfort'. Page 3 of the leavepiece was headed '… and the comfort they desire' and featured a bar chart using data reported in Vold *et al*. The bar chart was headed 'Patients Reported Greater Discomfort with Cosopt than with Azarga Suspension'. A claim above the bar chart read 'Significantly more comfortable than Cosopt Solution'. The bar chart plotted mean ocular discomfort score on a scale from 0 (no discomfort) to 4 (very severe discomfort) and showed that at week 1 the mean ocular discomfort score for Azarga (n=48) was 0.77 (1 = mild discomfort) and that for Cosopt (n=47) was 1.53 (2 = moderate discomfort). This difference was statistically significant (p=0.0003). Vold et al reported that the distribution of the ocular discomfort scores at week 1 for Azarga was: 0 (no discomfort), 48.9%; 1 (mild discomfort), 34%; 2 (moderate discomfort), 10.6%; 3 (severe discomfort), 4.3% and 4 (very severe discomfort), 2.1%. The comparable distribution of scores for Cosopt was: 0, 14.9%; 1, 38.3%; 2, 27.7%; 3, 17% and 4, 2.1%. The Panel thus considered that although there was a greater likelihood of feeling discomfort following the instillation of Cosopt vs Azarga, 34% of Azarga patients nonetheless reported mild discomfort with Azarga and 17% reported moderate to very severe discomfort. The comparable scores for Cosopt were 14.9% and 46.8%.

The Panel considered that the repeated references to comfort in the leavepiece might be seen as implying that there was no discomfort at all with Azarga which was not so for 24 out of the 47 patients evaluated; one of those patients reported very severe discomfort. The Panel noted that the Azarga SPC stated that eye pain, eye irritation and foreign body sensation in the eyes were common (≥1/100 to <1/10) adverse reactions. Ocular discomfort as defined by Vold *et al* was any of the following: burning, stinging, a feeling heat or warmth, sharp pain or smarting pain. Vold *et al* did not include foreign body sensation in their definition of ocular discomfort.

The Panel considered that the claim 'Significantly more comfortable than Cosopt Solution' was exaggerated as alleged and did not reflect the evidence. Vold *et al* had evaluated the ocular discomfort of Azarga and Cosopt and the claim should reflect this. A breach of Clauses 7.2 and 7.10 was ruled. The claim had not been substantiated. A breach of Clause 7.4 was ruled.

The Panel further considered that the repeated use of comfort/comfortable was exaggerated, all embracing and misleading as alleged. A breach of Clauses 7.2 and 7.10 was ruled.

The Panel did not consider that the failure to note that Vold *et al* and Mundorf *et al* measured transient post-instillation discomfort misleadingly implied that the discomfort might be longer lasting and therefore more clinically significant as alleged. No breach of Clause 7.2 was ruled.

The Panel noted that 'comfort' was not defined in the leavepiece. The two studies cited in support of comfort claims (Vold *et al* and Mundorf *et al*) had, in fact, assessed discomfort. Vold *et al* had defined discomfort as any one of burning, stinging, a feeling of heat or warmth, sharp pain or smarting pain, and asked patients to evaluate any such discomfort on a scale of 0 – 4 (none – very severe). Mundorf *et al* had not described what was meant by discomfort but had asked patients to complete an ocular discomfort scale (0 (no discomfort) to 9 (substantial discomfort)) approximately one minute after treatment and to complete a preference question. Although noting its ruling above regarding the use of the word 'comfort', the Panel nonetheless considered that it was misleading as alleged not to define the term. The Panel considered that the leavepiece was misleading and exaggerated as alleged. A breach of Clauses 7.2 and 7.10 was ruled.

With regard to blurred vision, the Panel noted that it was a common side-effect with both Azarga and Cosopt. Although inconvenient for the patient, the Panel did not consider that blurred vision was a discomfort factor; it was something a patient experienced rather than felt. Thus, in the context of a discussion about the relative discomfort of Azarga and Cosopt, the Panel did not consider that it was misleading not to refer to blurred vision as alleged. No breach of Clause 7.2 was ruled in that regard.

APPEAL BY ALCON

Alcon disagreed with the Panel's ruling and was concerned that the ruling did not refer to the evidence it had submitted in its response. It was difficult to be clear of the exact reasoning behind the conclusions reached. Nevertheless, Alcon submitted that the Panel's ruling was incorrect on all counts based on the relevance and appropriateness of the claims and the available evidence. The Panel's conclusions did not respect the knowledge and experience of the target audience to which the leavepiece was directed and did not recognise Alcon's right to promote legitimate, relevant and demonstrable differences between Azarga and the brand market leader, Cosopt.

Alcon submitted that the main difference between the two eye drops was that of comfort. This difference was confirmed in two studies, specifically designed to assess comparative comfort (Vold *et al*

and Mundorf *et al*). Alcon's definition of comfort/comfortable was in line with its target audience's definition. Ophthalmologists were experienced in treating patients with OAG/ocular hypertension and very familiar with 'comfort' as it applied to eye drops and with the importance that their patients attached to the concept. This was confirmed in the views expressed by a number of ophthalmologists experienced in the field of glaucoma and previously provided by Alcon.

Alcon submitted that as a matter of natural language it was clear that 'comfort' and 'discomfort' were two sides of the same coin and that 'more comfortable' was synonymous with 'less uncomfortable' (or 'less discomfort') ie, a question of perspective: glass half empty/glass half full were the same thing. Experts in the field used the terminology interchangeably. Accordingly, Alcon's use of 'comfort' complied with their understanding and was therefore not all-embracing or misleading by exaggeration or otherwise. Alcon's ability to promote the difference in comfort that had been demonstrated between Cosopt and Azarga was clinically justified and important. If the Panel's decision was upheld, then Alcon submitted that it would not be able to promote this difference in an accurate or reasonable manner.

Alcon noted that the Code applied to the promotion of medicines to members of the health professions and to appropriate administrative staff. Thus Clauses 7.2, 7.4 and 7.10 only applied as they related to the promotion of medicines to the relevant professional target group outlined and that their interpretation was intended to respect the special experience and understanding of this group. Promotional material should be judged for compliance with the Code based on the target audience's ie ophthalmologists' understanding of the matters covered and not from a non specialist's point of view. The leavepiece at issue, was directed to ophthalmologists who treated patients with glaucoma or ocular hypertension. The management and treatment of glaucoma patients was entirely dealt with in the hospital ophthalmic department and since Alcon only employed a specialist hospital sales force, the target audience for the leavepiece was clearly defined.

Alcon submitted that although the Panel's ruling of a breach of Clause 7.2, 7.4 and 7.10 in relation to the claim 'Significantly more comfortable than Cosopt Solution' was preceded by considerable discussion about the data presented in Vold *et al* and about adverse events listed in the SPC for Azarga, there was no suggestion that this had specifically influenced the Panel's conclusions on this point. However, the Panel noted that Vold *et al* had evaluated the ocular discomfort of Azarga and Cosopt and the claim should reflect this. Alcon therefore assumed that this was the primary reason why the Panel considered that this quote was exaggerated, did not reflect the evidence and had not been substantiated. The title of Vold *et al* was 'A One-Week Comfort Study of BID-Dosed Brinzolamide 1%/Timolol 0.5% Ophthalmic Suspension Fixed Combination Compared to BID-Dosed Dorzolamide 2%/Timolol 0.5% Ophthalmic Solution in Patients with Open-Angle Glaucoma or Ocular Hypertension' (emphasis added). The study was published in the Journal of Ocular Pharmacology and Therapeutics, a peer reviewed and respected ophthalmic journal. The stated aim of the study was to evaluate the ocular discomfort of Azarga vs Cosopt in a group of 95 glaucoma or ocular hypertensive patients. Patients had their current glaucoma therapy assessed on a five point discomfort scale and were then switched to either Azarga or Cosopt, twice daily, and then assessed the trial product on the same discomfort scale after one week of dosing. The mean discomfort score for patients treated with Azarga was 0.77, while for Cosopt it was 1.53, (p=0.0003). The authors concluded that, Azarga was associated with a statistically significant less ocular discomfort profile than Cosopt. This claim could hardly be contested as it was reproduced in the Azarga SPC '(in three controlled clinical trials, the ocular discomfort upon instillation of Azarga was significantly lower than that of Cosopt'). Presumably, therefore, the Panel could not have considered the claim 'Significantly less discomfort than Cosopt' to be in breach of Clauses 7.2, 7.4 and 7.10. However 'comfort' and 'discomfort' were interchangeable (ie less discomfort equated to more comfort). There was no logical difference in meaning between this claim and the claim made, 'Significantly more comfortable than Cosopt' for the following reasons:

- Comfort and discomfort were not absolute terms but were subjective and linguistically they were opposites, such that an increase in discomfort must logically and inevitably result in a decrease in comfort. It was therefore not misleading or inaccurate to conclude that if a product was less uncomfortable (less discomfort) than another, it must be more comfortable. It should be recognised that the claim, 'Significantly more comfortable than Cosopt' did not seek to claim or imply that Azarga was a comfortable solution or would never cause discomfort, it was merely an accurate comparative statement supported by all of the available data.

- Although Vold *et al* used a 'discomfort scale' and expressed their results in terms of comparative discomfort, it was clear that the authors also considered this to be a measure of comparative comfort and indeed that comparative comfort was their primary interest:

    - The title of the published paper began, 'A One-Week **Comfort** Study…' (emphasis added)

    - The 'Methods' section stated, 'These parameters and the discomfort scale were the same as those used in a published study comparing the **comfort** of brinzolamide and dorzolamide' (emphasis added).

- The 'Statistical Analysis' section stated 'The primary statistical aim of this study was to demonstrate that the **ocular comfort** of (Azarga) dosed twice daily is superior to that of (Cosopt) dosed twice daily' (emphasis added).

- The 'Discussion' section stated, 'The results of this clinical trial demonstrate that the **ocular comfort** of (Azarga) dosed twice daily is superior to that of (Cosopt) dosed twice daily in patients with open-angle glaucoma or ocular hypertension' (emphasis added).

Alcon submitted that ocular discomfort scales were relatively commonly used in the ophthalmic literature to assess the comparative comfort of ophthalmic products and 'discomfort' and 'comfort' were used interchangeably. Evidence to support this contention, in the form of published references and expert testimony, was provided to the Panel. Therefore the claim, 'More comfortable than Cosopt', accurately reflected Vold *et al*; was consistent with the conclusions and intentions of the authors and would not be considered exaggerated, misleading or unsubstantiated by the target audience for the leavepiece, ie glaucoma specialists.

Alcon submitted that in any event, it should be recognised that in Vold *et al*, the mean discomfort score for subjects receiving Azarga was 0.77 and for Cosopt was 1.53 on a scale ranging from 0 to 4. In other words, both of these products (particularly Azarga) were judged to be far closer to the 'no discomfort' end of the scale than to the 'severe discomfort' end. In a similar study (Mundorf *et al*), the comparative comfort of Azarga and Cosopt was assessed on a 10 point discomfort scale (0= no discomfort to 9= severe discomfort). In this study, the mean discomfort scores were 1.4 and 2.9 for Azarga and Cosopt respectively; again heavily skewed towards the lower 'no discomfort' end of the scale. It was therefore more relevant and more representative to refer to a difference in comfort rather than in discomfort.

Alcon submitted that it was also relevant that no attempt had been made to disguise the nature of and evidence behind the claim 'more comfortable than Cosopt'. In the leavepiece this claim was made immediately above a bar chart that clearly represented 'mean discomfort scores' taken from Vold *et al* and the discomfort scale used was also included.

Alcon submitted that although it was not made clear in its ruling, it suspected that the Panel's consideration of this claim was affected by its general views on the use of the words comfort/comfortable as they applied to Azarga. These views would be considered below. However, regardless of the outcome of the appeal below, this ruling should be considered as an independent matter and that the claim, 'more comfortable that Cosopt', was not exaggerated, was an accurate reflection of the data and had been adequately substantiated. It was therefore not in breach of Clauses 7.2, 7.4 and 7.10.

Alcon noted that the Panel further considered that the repeated use of comfort/comfortable was exaggerated, all embracing and misleading as alleged. A breach of Clauses 7.2 and 7.10 was ruled. Alcon submitted that the justification for this ruling was not made clear. The Panel's ruling not only reflected an unnecessarily negative and inaccurate interpretation of the data presented but also indicated that the Panel might not be sufficiently familiar with glaucoma practice.

Alcon submitted that the Panel chose to characterise the data from Vold *et al* by stating that 17% of patients receiving Azarga reported mild to very severe discomfort. In fact, only 6.4% of patients reported severe or very severe discomfort, while 82.9% of patients reported no or mild discomfort. Almost half of all patients receiving Azarga (48.9%) reported no discomfort. The instillation of eye drops was generally a fairly unpleasant experience. The results obtained by Vold *et al* in patients who had previously been stabilised on other glaucoma medications (in some cases only used once daily rather than twice daily as with Azarga), which they would have been acclimatised to, when switched to a completely new eye drop and then assessed after only one week of use were considered to be excellent and demonstrated that Azarga could be described as a 'comfortable' product. The comparative results for Cosopt also demonstrated that Azarga could be considered by the ophthalmologists to be 'comfortable' when compared to the market leader in this sub-sector. The fact that the mean discomfort score for both test products was significantly higher than the baseline score did not indicate that Azarga could be considered to be 'uncomfortable', since the results were not truly comparable. The baseline figure represented the score given by the patient for an established therapy, which they had become used to, possibly over a long period of time, while the score for the test products represented a score given to a new 'trial' product. To obtain a fair comparison, an evaluation of the initial therapy should have been made in a double-masked fashion after a washout period. However, the comparison between the scores obtained with Cosopt and Azarga was valid.

Alcon submitted that the Panel also seemed to have considered that the listing of eye pain, eye irritation and foreign body sensation in the Azarga SPC had particular relevance to the use of the words comfort/comfortable. This represented a distortion of the situation with glaucoma therapy. The SPCs of eye drops commonly used in glaucoma, where incidence of adverse events was included in the SPC, all listed symptoms of discomfort as common or very common adverse effects. Indeed, the SPCs of artificial tear preparations, products designed specifically to improve the comfort of dry eyes, found similar results, although, due to lack of controlled clinical studies with some older products,

details on the incidence of the side effects were sometimes not available. Alcon submitted the reported incidence of comfort related side effects listed in the SPCs of a number of glaucoma products and artificial tears (as defined by Vold *et al*).

Alcon submitted that in the two large long-term studies referenced in the leavepiece (Manni *et al* and Kaback *et al* (2008)) the reported incidence of these three adverse effects (eye pain, eye irritation and foreign body sensation) was towards the low end of the range defined by the term 'Common side effects' as shown in the table below.

Study	Product	Eye pain	Eye irritation	Foreign body sensation
Manni *et al* (n=220)	Azarga	2.7%	2.7%	1.4%
	Cosopt	6.5%	10.6%	0.5%
Kaback *et al* (n=174)	Azarga	1.1%	2.9%	0.6%
	Timolol	1.1%	3.4%	0.6%

Alcon submitted that these figures clearly indicated the comparatively low level of such complaints reported with Azarga. The comparison with the results obtained with timolol in Kaback *et al* were particularly revealing, since timolol had for a long time, been the treatment of first choice for many glaucoma patients and represented the standard against which other treatments were generally judged.

Alcon submitted that it was therefore unreasonable for the Panel to suggest that Azarga could not be classified as 'comfortable' compared with Cosopt based on the comments that it had made in its review of the data. Comfort and discomfort were subjective, relative terms that were commonly used in ophthalmology and were well understood by the glaucoma specialist who routinely dealt with patients using eye drops on a long-term basis. Expert testimony to this effect had been provided to the Panel. The Panel was therefore wrong to suggest that the repeated references to comfort in the leavepiece might be seen as implying that there was no discomfort at all with Azarga. This suggestion was inaccurate and could not be justified in relation to the target audience and took inadequate account of their knowledge and experience.

Alcon submitted that within the field of glaucoma therapy, the available data was consistent with the description of Azarga as a comfortable solution. The repeated use of comfort/comfortable in the leavepiece was not in breach of Clauses 7.2 and 7.10.

Alcon noted that the Panel had considered it misleading not to define the term 'comfort' in breach of Clauses 7.2 and 7.10. Alcon submitted that 'comfort' was commonly used by ophthalmologists working with glaucoma patients and was well understood. This was illustrated by expert testimony provided to the Panel and was also evidenced by the fact that it was often considered that 'comfort' and 'discomfort' did not need to be defined in the ophthalmic literature. An example of this was provided by Mundorf *et al* as quoted by the Panel, but other examples were provided in Alcon's response above. It was therefore not necessary to define 'comfort' in a leavepiece directed solely to this target audience. Under these circumstances, failure to define the term was not in breach of Clauses 7.2 and 7.10.

In summary, Alcon submitted that this case should not have come before the Panel if Merck Sharp & Dohme had accepted the target audience's and patients' definition of comfort as intended within the leavepiece.

COMMENTS FROM MERCK SHARP & DOHME

Merck Sharp & Dohme stated that Alcon did not appear to have used any substantive additional arguments to support its appeal.

In relation to the claim 'Significantly more comfortable than Cosopt Solution' Merck Sharp & Dohme noted that Alcon had repeated its assertion that Vold *et al* showed a significant difference in favour of Azarga but continued to ignore that the report showed the majority of Azarga study subjects reported discomfort. Considerations such as the use of the word comfort in the study's title, in the Methods, Statistical Analysis and Discussion sections of the report, and its interchangeability or otherwise with discomfort made no difference to Merck Sharp & Dohme's allegation that a claim for superior ocular comfort was misleading on the basis of the supporting scientific evidence.

Merck Sharp & Dohme continued to allege that a claim for Azarga, a product producing significant levels of discomfort in most patients, being more comfortable than a competitor was misleading. It was regrettable that many of the active constituents in topical glaucoma treatments caused post-instillation discomfort, if this affected only a minority of patients 'more comfort' claims might be acceptable. While the situation remained as it was Merck Sharp & Dohme disagreed with Alcon's contention that 'more comfort' and 'less discomfort' should be interchangeable. Merck Sharp & Dohme therefore agreed with the Panel that there had been breaches of Clauses 7.2, 7.4 and 7.10.

Merck Sharp & Dohme noted that in relation to the repeated use of comfort/comfortable, Alcon had repeated its previous arguments in support of its comfort claim. In doing so it had overlooked the implication in the leavepiece that a product causing significant discomfort in the majority of patients was comfortable. This implication had been achieved by the repeated use of 'comfort' or 'comfortable'. Such overuse of this phraseology in this context constituted a misleading claim that was also exaggerated or all-embracing. Merck Sharp & Dohme therefore agreed with the Panel that there had been breaches of Clauses 7.2 and 7.10.

Merck Sharp & Dohme alleged that the use of claims based on comfort or comfortable in this context, relying on scientific data such as that presented by Vold et al or Mundorf *et al*, was misleading if no attempt was made to define the terminology used. Once again Alcon had relied on verbatim comments from selected experts to support its contention that comfort was a widely-understood concept in this therapy area. However, ophthalmologists used a variety of topical products to treat numerous other conditions besides glaucoma. An assumption that a prescriber would immediately appreciate the specific post-instillation discomfort issues when viewing the Azarga leavepiece and use this knowledge in interpreting the data appropriately without adequate further explanation was unfounded. Merck Sharp & Dohme therefore agreed with the Panel that there had been breaches of Clauses 7.2 and 7.10.

APPEAL BOARD RULING

The Appeal Board noted that page 3 of the leavepiece featured a bar chart using data from Vold *et al*. The bar chart was headed 'Patients Reported Greater Discomfort with Cosopt than with Azarga Suspension'. The claim at issue 'Significantly more comfortable than Cosopt Solution' appeared above the bar chart. The bar chart plotted mean ocular discomfort score on a scale from 0 (no discomfort) to 4 (very severe discomfort) and showed that at week 1 the mean ocular discomfort score for Azarga (n=48) was 0.77 (1 = mild discomfort) and that for Cosopt (n=47) was 1.53 (2 = moderate discomfort). This difference was statistically significant (p=0.0003). Vold *et al* reported that the distribution of the ocular discomfort scores at week 1 for Azarga was: 0 (no discomfort), 48.9%; 1 (mild discomfort), 34%; 2 (moderate discomfort), 10.6%; 3 (severe discomfort), 4.3% and 4 (very severe discomfort), 2.1%. The comparable distribution of scores for Cosopt was: 0, 14.9%; 1, 38.3%; 2, 27.7%; 3, 17% and 4, 2.1%.

The Appeal Board noted that Vold *et al* (a peer reviewed study) aimed to evaluate ocular discomfort and concluded that Azarga was associated with a statistically significantly less ocular discomfort profile than Cosopt. Although the authors evaluated ocular discomfort the title of Vold *et al* was 'A One-Week Comfort Study …'. In the statistical analysis section Vold *et al* stated that 'The primary statistical aim of this study was to demonstrate that the ocular comfort of [Azarga] dosed twice-daily is superior to that of [Cosopt] dosed twice-daily'. Similarly the discussion section stated that 'The results of this clinical trial demonstrate that the ocular comfort of [Azarga] dosed twice-daily is superior to that of [Cosopt] dosed twice-daily in patients with open-angle glaucoma or ocular hypertension'. It appeared that Vold *et al* had used 'comfort' and 'discomfort' interchangeably.

The Appeal Board noted that the Azarga SPC stated that 'In three controlled clinical trials, the ocular discomfort upon instillation of Azarga was significantly lower than that of [Cosopt]'. Vold *et al* was one of the three studies referred to (the others being Manni *et al* and Mundorf *et al*).
The Appeal Board considered that the claim that Azarga was 'Significantly more comfortable than Cosopt Solution' was not inconsistent with Vold *et al* or the Azarga SPC. The claim headed a bar chart which provided the relevant data from Vold *et al*. The Appeal Board did not consider that the claim was misleading or exaggerated; it was capable of substantiation. The Appeal Board therefore ruled no breach of Clauses 7.2, 7.4 and 7.10. The appeal on this point was successful.

The Appeal Board noted that other uses of 'comfort' and 'comfortable' were not within the context of a comparison with Cosopt; the terms were used as absolutes. These included the front page of the leavepiece headed 'Find comfort in our strength' which featured the claim 'New Azarga Suspension brings you the strength you would expect, with the comfort your patients deserve'. The product logo in the bottom right-hand corner included the strapline 'Where strength meets comfort'. Page 3 of the leavepiece was headed '… and the comfort they desire'. Pages 4 to 8 also included general claims for 'comfort' per se and/or the product logo and strapline. The Appeal Board considered that the cumulative effect of the repeated references to comfort and/or comfortable, as absolutes, in the leavepiece might be seen as implying that there was no discomfort at all with Azarga which was not so. Many patients with glaucoma were asymptomatic and therefore using eye drops twice a day would not be considered comfortable. Also Vold *et al* reported that with Azarga for 24 out of the 47 patients evaluated one of those patients reported very severe discomfort and over half of all the patients reported some level of discomfort (mild 34%, moderate 10.6%, severe 4.3% and very severe 2.1%). The Appeal Board noted that the Azarga SPC stated that eye pain, eye irritation and foreign body sensation in the eyes were common (≥1/100 to <1/10) adverse reactions. Ocular discomfort as defined by Vold *et al* was any of the following: burning, stinging, a feeling of heat or warmth, sharp pain or smarting pain. Vold *et al* did not include foreign body sensation in their definition of ocular discomfort.

The Appeal Board considered that the repeated use of 'comfort' and/or 'comfortable' was exaggerated, all embracing and misleading as alleged. The Appeal Board upheld the Panel's ruling of a breach of Clauses 7.2 and 7.10. The appeal on this point was unsuccessful.

The Appeal Board noted that 'comfort' was not defined in the leavepiece; the two studies cited in support of comfort claims (Vold *et al* and Mundorf *et al*) had evaluated discomfort. Vold *et al* had defined discomfort as any one of burning, stinging, a feeling of heat or warmth, sharp pain or smarting pain, and asked patients to evaluate any such

discomfort on a scale of 0 – 4 (none – very severe). Mundorf *et al* had not described what was meant by discomfort but had asked patients to complete an ocular discomfort scale (0 (no discomfort) to 9 (substantial discomfort)) approximately one minute after treatment and to complete a preference question. The Appeal Board noted that the Azarga SPC had not defined discomfort in the statement 'In three controlled clinical trials, the ocular discomfort upon instillation of Azarga was significantly lower than that of [Cosopt]'.. The Appeal Board noted that the third clinical trial referred to, Manni *et al* was, unlike the other two (Vold *et al* and Mundorf *et al*), a safety and efficacy trial comparing Azarga and Cosopt. In Manni *et al* the only adverse event that occurred with a statistically significantly different frequency between the two treatment groups and that contributed to the meaning of discomfort was ocular irritation; six patients in the Azarga group (n=220) reported eye irritation vs twenty three in the Cosopt group (n=217), p=0.0009.

The Appeal Board noted that the intended audience was an important consideration. In this instance ophthalmologists would understand what comfort meant for their glaucoma patients; Alcon had provided comments from ophthalmologists to support its submission. The Appeal Board considered that it was not misleading as alleged not to define 'comfort' in the leavepiece. The Appeal Board considered that the leavepiece was not misleading or exaggerated in this regard. No breach of Clauses 7.2 and 7.10 were ruled. The appeal on this point was successful.

Complaint received **17 December 2009**

Case completed **12 May 2010**