CASE AUTH/2389/2/11

ALLERGAN v ALCON

Promotion of Travatan

Allergan complained about a promotional campaign for Travatan (travaprost preserved with Polyquad) by Alcon which featured the picture of a vertical, long-stemmed rose with no thorns; thirteen thorns lay around the base of the stem. An advertisement featuring the image had appeared in the British Journal of Ophthalmology.

The detailed response from Alcon is given below.

Allergan submitted that the campaign visual was clearly a comparative image – implying that other products in the same therapeutic category, such as its product Lumigan (bimatoprost), had 'thorns' whilst Travatan had none. The clear implication was of an improved ocular safety profile and potentially a complete lack of ocular adverse events.

In inter-company dialogue, Alcon had submitted that the thornless rose was a comparative image, but only in as much as it was intended to represent a comparison with the original formulation of Travatan preserved with benzalkonium chloride (BAK).

Allergan knew of only one clinical study comparing Travatan preserved with Polyquad with Travatan preserved with BAK (Denis *et al* 2010) which demonstrated that the safety profile was similar for both products.

Allergan alleged that the visual was misleading in breach of the Code.

The Panel noted the picture of the thornless rose which ran down the left hand side of the advertisement. The prominent headline in the top right hand corner was 'Introducing BAK-free formulation Travatan'. In the Panel's view, most readers would associate the picture of the rose with the prominent headline and thus see the rose as representing Travatan without BAK.

The Panel considered that thorns on a rose stem would be seen as something injurious; the advertisement implied that Travatan preserved without BAK was free of such hazard.

The Panel noted that Travatan preserved with Polyquad was still associated with one of the ocular side-effects referred to in Section 4.4, Special warnings and precautions for use, of the summary of product characteristics (SPC) for Travatan preserved with BAK. Further, Section 4.8 of the SPC for Travatan preserved with Polyquad listed another ten possible ocular adverse events which were also listed as possible adverse events in the SPC for Travatan preserved with BAK. In this regard the Panel did not consider that the thornless rose was a fair reflection of the side effect profile of Travatan preserved with Polyquad compared with Travatan preserved with BAK. The advertisement was misleading and exaggerated the difference between the two. Breaches of the Code were ruled which were upheld on appeal. The Appeal Board, *inter alia*, noted the findings of Denis *et al* and considered that the visual was misleading and exaggerated the difference between the two formulations of Travatan as alleged.

The Panel did not consider that the thornless rose implied a potentially complete lack of side-effects as alleged; no breach of the Code was ruled.

The Panel did not consider that the visual in the advertisement implied any comparison with competitor products as alleged. No breach of the Code was ruled.

Allergan alleged that the claim 'Travatan BAK-free', used to alert customers to the newly formulated Travatan, misleadingly implied that the product was preservative-free, when in fact it was preserved with Polyquad. This preservative was clearly not 'side-effect free' as was generally implied in the advertisement and with the campaign visual. Allergan also considered the use of laboratory studies within the advertisement was unacceptable to support general claims regarding tolerability. Allergan was not aware of any clinical data to support the tolerability claims for Polyquad compared with BAK.

The Panel did not consider that the claims that Travatan was BAK-free implied that it was also preservative-free. The advertisement clearly referred to 'A multidose prostaglandin analogue with POLYQUAD'. The Panel did not consider that the claims were misleading as alleged. No breach of the Code was ruled.

The Panel noted that the advertisement included, *inter alia*, the claims 'Contains Polyquad, which had demonstrated a gentler effect on the ocular surface than BAK in laboratory studies' and 'Significantly less toxic to human conjunctive and coneal epithlial cells when compared to latanoprost solutions (preserved with 0.02% BAK *in vitro*)'. Both claims were referenced to animal or *in vitro* studies. The Code stated that care must be taken so as not to mislead with regard to the significance of such studies. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance significance.

The Panel considered that the animal and *in vitro* studies cited in the advertisement implied that BAK-free Travatan had a better safety profile compared with Travatan preserved with BAK. The only direct clinical comparison of the two (Denis *et al*) did not show that to be the case. The Panel considered that the advertisement was misleading and exaggerated in that regard. Breaches of the Code were ruled. High standards had not been maintained. A further breach of the Code was ruled. Alcon appealed these rulings.

The Appeal Board noted that under the heading 'Travatan BAK-free formulation:' the advertisement featured two bullet points which referred to animal and *in vitro* studies. In particular the claim 'Significantly less toxic to human conjunctive and corneal epithelial cells when compared to latanoprost solutions (preserved with 0.02% BAK *in vitro*)' was referenced to a study which compared the effects of Travatan BAK-free with travoprost and lantaprost which were both preserved with BAK on isolated human conjunctival epithelial cells. The Appeal Board noted that the authors stated that '…formulations preserved with Polyquad *might* be better for ocular surface health than solutions containing BAK' (emphasis added). In the Appeal Board's view 'Significantly less toxic…' as used in the advertisement was quite different to '…might be better…', as used in the study. The Appeal Board considered that in that regard the claim did not reflect the cited paper.

The Appeal Board considered that although the results of *in vitro* models might predict future clinical effects there was no guarantee that this would be so. When presenting animal and *in vitro* studies care was needed to ensure that, in the absence of clinical evidence, clinical effects were not inferred or claimed. The Appeal Board noted that the only clinical evidence available concluded that the safety profile of Travatan preserved with Polyquad was similar to that preserved with BAK.

The Appeal Board considered that the *in vitro* and animal data presented in the advertisement implied that BAK-free Travatan was better tolerated than that preserved with BAK and this was not supported by the available clinical data. The Appeal Board considered that the advertisement was misleading and exaggerated in that regard. The Appeal Board upheld the Panel's ruling on this point. The Appeal Board further considered that high standards had not been maintained and it upheld the Panel's ruling in this regard.

Allergan Limited complained about the promotion of Travatan (travaprost preserved with Polyquad) by Alcon Laboratories (UK) Limited. The complaint concerned a campaign which featured a picture of a vertical, single, long-stemmed rose in full bloom. Thirteen thorns lay around the base of the stem. An advertisement (ref TBF:AD:12/10:LHC) had appeared in the British Journal of Ophthalmology.

1 Campaign visual – A rose without thorns

COMPLAINT

Allergan noted that the Travatan campaign visual was a rose that had lost all of its thorns. The use of a rose without thorns was clearly a comparative image – implying that other products in the same therapeutic category, such as its product Lumigan (bimatoprost), had 'thorns' whilst Travatan had none. The clear implication was of an improved ocular safety profile and potentially a complete lack of ocular adverse events.

In inter-company dialogue Alcon had submitted that the rose without thorns was a comparative image, but only in as much as it was intended to represent a comparison with the original formulation of Travatan preserved with benzalkonium chloride (BAK). Allergan did not agree with this interpretation; even if this were the case there was a clear implication of an improved safety profile for Travatan preserved with Polyquad vs Travatan preserved with BAK. The implication of an improved safety profile vs the previous formulation was not supported by the clinical evidence.

Allergan knew of only one clinical study, published as an abstract and a poster, which compared Travatan preserved with Polyquad with Travatan preserved with BAK (Denis *et al* 2010). The study demonstrated that the safety profile was similar for both products. Indeed, the authors concluded that 'the safety profile of travoprost BAK free was similar to that of travoprost BAK'. The summary of product characteristics (SPC) for the BAK free formulation also listed eye irritation, dry eye, pruritus, eye pain and ocular discomfort as common undesirable effects.

Alcon had not supplied any additional clinical data which compared Travatan preserved with Polyquad and Travatan preserved with BAK to support the implication of an improved safety profile as illustrated by the visual.

Allergan alleged that the visual was misleading in breach of Clauses 7.2, 7.3 and 7.10.

RESPONSE

Alcon stated that it had reformulated Travatan by replacing the preservative BAK with Polyquad. Alcon no longer intended to market the BAK formulation of Travatan and therefore its promotional campaign raised awareness of the new formulation; the visual of a rose without thorns symbolised the difference between the old and new formulations of Travatan. The entire campaign was centred on this theme, and when the image was viewed in conjunction with the surrounding text there was no confusion as to the meaning. The material merely showed that Travatan was now BAK-free.

The decision to reformulate Travatan and replace BAK with Polyquad was based on extensive clinical and experimental data testifying to the particular risk of BAK causing eye irritation. BAK was the most widely used preservative in ophthalmic preparations for the treatment of glaucoma as it exhibited efficacious antimicrobial properties, yet its toxicity to the cornea and potential to damage the ocular surface had been well documented in the literature. In addition, a number of patients were allergic to BAK and confined to using single-dose preservative-free medicines. The particular problems associated with BAK, which were widely known within the ophthalmic community, were reflected in the special warning in Section 4.4 of the SPCs for all ophthalmic products containing BAK to the effect that BAK could cause punctate keratopathy and/or toxic ulcerative keratopathy. This warning was additional to the list of undesirable effects. The European Medicines Agency (EMA) did not require the inclusion of an equivalent special warning in the SPC or leaflet for the BAK-free version of Travatan. This clearly supported the position that BAK had a particular association with severe forms of eye irritation, whereas Polyquad, which had been used as a preservative in many ophthalmic formulations over the past 20 years or more, did not. Alcon believed that this testified to a real difference between the original and new formulations of Travatan. Indeed, the absence of BAK was an essential characteristic of the new formulation, and Alcon considered it appropriate and necessary to highlight this difference to ophthalmologists when promoting the new formulation of Travatan.

As the new formulation would completely replace the original formulation of Travatan, the purpose of the current marketing campaign was to announce and explain this important change to customers. The rose without thorns portrayed the difference between the original and new formulations and non-ambiguous accompanying text stated that Travatan was now BAK-free. The rose without thorns was a comparative image between the original formulation of Travatan and the new BAK-free formulation. The thorns represented the known ocular irritant, BAK. The new formulation of Travatan no longer contained BAK and therefore was 'thorn' free. This reflected the position in the SPC which showed that Travatan no longer contained BAK and the special warning in Section 4.4 of the SPC had been removed.

Alcon did not agree that the image, in its proper context, implied that the new formulation of Travatan had a complete lack of ocular adverse events or that overall it had an improved ocular safety profile. The visual (and the accompanying text) made it clear that the focus of the promotional material was to announce the removal of the particular irritant, BAK, from Travatan. In addition, the audience to whom the material was directed was well acquainted with glaucoma medicines and their side effects. Moreover, the safety profile of Travatan was unequivocally apparent from the prescribing information included in all materials and the SPC which was either available from the sales representative or via the electronic medicines compendium.

Alcon noted Allergan's reference to Denis *et al* in support of its allegation that the material was misleading and suggested that Travatan (BAK-free) had an improved ocular safety profile compared with Travatan preserved with BAK. However, as explained above, the rose without thorns image did not imply that overall Travatan had an improved ocular safety profile. Further, and in any event, Denis *et al* was a non-inferiority study and could therefore not have been expected to show the effects of long-term exposure to BAK. The particular problems with BAK were known to arise from chronic use; however Denis *et al* was only conducted over a period of three months and so could not have shown the effects of chronic use. Nevertheless, studies had shown that long-term use of BAK could be associated with undesirable adverse effects. It was also known that the use of BAK-free ophthalmic medicines could reverse previous ocular damage caused by BAK. Further to this, *in vivo* (animal) and *in vitro* cytotoxicity studies had shown that Polyquad was less toxic and less damaging to the ocular surface than BAK.

Alcon therefore considered the rose without thorns image, which must be viewed in its proper context by reference to the surrounding text and in light of the intended audience, complied with the Code, including Clauses 7.2, 7.3 and 7.10 (which Allergan cited without application to the facts):

- The image was not misleading as to the safety profile of the new Travatan formulation. The intended audience of ophthalmologists was well aware of the particular problems associated with the known ocular irritant, BAK, which was appropriately represented by thorns. The new formulation of Travatan no longer contained BAK and was therefore 'thorn' free. The image was therefore accurate, and not misleading.

- The image was not a misleading comparison between Alcon's product and a competitor's product; it unambiguously compared the original formulation of Travatan and the new BAK-free formulation – nothing more. The feature compared between the two formulations of Travatan (namely the presence/absence of BAK) was material, relevant and not misleading.

- The image was objective and did not exaggerate the properties of Travatan. The image was an appropriate metaphor for the absence of BAK in the new formulation, which was appropriately represented by thorns because BAK was a known ocular irritant, as supported by the literature and the special warning in the SPC. Therefore, the image did not imply that Travatan (BAK-free) had some special merit, quality or property which had not been substantiated.

Alcon therefore strongly disagreed with Allergan's interpretation of the rose without thorns image and considered its conclusions to be unfounded and alarmist.

PANEL RULING

The Panel noted that the complaint concerned the campaign visual of a thornless rose which presumably appeared on several promotional pieces. The Panel however, could not make an overarching ruling on material it had not seen and it thus considered the allegation solely in relation to the only piece provided by the complainant ie the advertisement at issue.

The Panel noted the picture of the thornless rose which ran down the left hand side of the advertisement. The prominent headline in the top right hand corner was 'Introducing BAK-free formulation Travatan'. In the Panel's view, most readers would associate the picture of the rose with the prominent headline and thus see the rose as representing Travatan without BAK.

The Panel considered that thorns on a rose stem would be seen as something injurious; the advertisement implied that Travatan preserved without BAK was free of such hazard. The Panel noted Alcon's submission about ophthalmic products containing BAK and the warning at Section 4.4 of their SPCs. The Panel noted that Section 4.4, Special warnings and precautions for use, of the SPC for Travatan preserved with BAK, included the statement '[BAK], which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since Travatan contains [BAK], close monitoring is required with frequent or prolonged use'. This statement was not in the BAK-free Travatan SPC although Section 4.8, Undesirable effects, of that SPC still listed punctate keratitis as a common (>1/100 to < 1/10) side effect of therapy. The Panel thus noted that Travatan preserved with Polyquad was still associated with one of the ocular side-effects referred to in Section 4.4 of the SPC for Travatan preserved with BAK. Further, Section 4.8 of the SPC for Travatan preserved with Polyquad listed another ten possible ocular adverse events which were also listed as possible adverse events in the SPC for Travatan preserved with BAK. In this regard the Panel did not consider that the thornless rose was a fair reflection of the side effect profile of Travatan preserved with Polyquad compared with Travatan preserved with BAK. The advertisement was misleading and exaggerated the difference between the two. A breach of Clauses 7.2, 7.3 and 7.10 was ruled.

The Panel did not consider that the thornless rose implied a potentially complete lack of side-effects as alleged; no breach of Clauses 7.2 and 7.10 was ruled.

The Panel did not consider that the visual in the advertisement implied any comparison with competitor products as alleged. No breach of Clause 7.3 was ruled.

APPEAL BY ALCON

Alcon appealed because, in its view, Allergan's complaint and the Panel's rulings of breaches of the Code were based, on a very limited view of the knowledge base relevant to the issues at hand, which were well known to, and appreciated by, those to whom the promotion of Travatan in general and the advertisement in particular was directed – ophthalomologists who specialised in the treatment of glaucoma. The complaint and rulings assumed a limited level of intelligence, knowledge and understanding that was incompatible with the target audience.

Alcon submitted that it reformulated Travatan because of the vast amount of experimental and clinical data available in the literature, and widely known to the ophthalmic community, about the potential ocular toxicity of long-term exposure to BAK, when used to preserve ophthalmic products. As a result of this data, labelling of all ophthalmic products preserved with BAK included a specific statutory warning to the effect that BAK might cause eye irritation. However, the realisation and understanding that the effects of BAK were more complex than this and more insidious had led to a greater interest in the use of alternative preservatives in ophthalmic products with the potential for long-term use, such as in glaucoma.

Alcon submitted that Baudouin (2008) was an excellent review about the detrimental effect of preservatives (particularly BAK) in eye drops and the implications for the treatment of glaucoma. The author made the following observations:

> 'In glaucoma, if effective, medical treatment is administered over the longterm, and therefore the majority of patients receive several decades of treatment. Based on data from clinical trials, the tolerability of glaucoma treatments seems satisfactory: few patients are withdrawn from medication as a result of local intolerance or allergy…..
>
> However, there are several major differences between clinical trials and the real-world progress of antiglaucoma therapy. Clinical trials are usually of short duration (6 months – 1 year). Patients with known hypersensitivity to the therapy or to the preservative contained within the product, and patients who have active ocular surface diseases such as dry eye, chronic allergy or severe blepharitis are often not included in such trials …. In population-based studies, the prevalence of dry eye in elderly patients (aged ≥ 65 years) varies between 15% and 34%... Impaired tear film may therefore interfere with topical treatments in a high proportion of patients, as the ocular surface disease may be encouraged by the drug(s) and/or preservatives, and may also reduce the resistance of the cornea and conjunctiva to the presence of toxic or irritant compounds.'

Allergan submitted that these observations were particularly relevant to this case, since they highlighted the fact that, although BAK was an acceptable ophthalmic preservative from a regulatory perspective, most ophthalmologists knew the limitations of regulatory studies and appreciated the more subtle effects that BAK might demonstrate in the long-term in a proportion of their patients. It was clear that problems with BAK were not universal and were a matter of degree, rather than being absolute. They could not therefore be considered simply with regard to the 'safety profile' of a product as indicated by the SPC or the results of regulatory studies designed to confirm currently acceptable levels of safety and efficacy but would only become apparent in appropriately designed, large, long-term studies, using appropriate assessment methods.

Numerous clinical studies had demonstrated the presence of ocular surface changes in glaucoma patients treated with BAK-containing medicines.

- A prospective epidemiological survey of 4107 glaucoma patients assessed the effects of preserved and preservative-free eye drops on ocular symptoms and conjunctival, corneal and palpebral signs in normal clinical practice (Pisella *et al* 2002). All symptoms of ocular surface disease (OSD) evaluated were significantly more prevalent in patients using preserved drops compared with those using preservative-free treatment. The prevalence of signs and symptoms was dose-dependent, increasing with the number of preserved eye drops used. In addition, when patients were either switched to preservative-free products or given fewer preservative-containing medicines, all symptoms and signs improved.

- Similar findings were obtained when pooled data from 9658 glaucoma patients were evaluated. The incidence of ocular signs and symptoms was significantly higher ($p<0.0001$) in patients receiving preserved eye drops, and it was observed that the incidence of these signs and symptoms could be decreased significantly ($p<0.0001$) by switching to a preservative-free formulation or by reducing the number of preservative-containing treatments (Jaenen *et al* 2007). Alcon noted that in this study and in Pisella *et al* (2002), the reference to preservative-containing treatments would almost certainly relate predominantly to products containing BAK since this was present in the vast majority of anti-glaucoma medications currently available. In the current edition of MIMS, of 25 other ocular hypotensive medicines listed, (excluding Travatan), 19 contained BAK, one contained benzododecinium bromide as the preservative and the other five were single dose, preservative-free preparations.

- A US study reported that 59% of patients with glaucoma or ocular hypertension had symptoms of OSD (Leung *et al* 2008). An association was demonstrated between the level of lissamine green staining of the conjunctiva, (an indicator of the presence of membrane damaged epithelial cells), and the number of BAK-preserved eye preparations, being used.

- A prospective observational study of 630 patients with primary open-angle glaucoma (POAG) or ocular hypertension, reported that 305 (48.4%) had mild, moderate or severe OSD symptoms (Fechtner *et al* 2010). OSD Index (OSDI) scores were significantly higher in those with a prior diagnosis of dry eye syndrome, but also varied with the number of IOP-lowering medications that were used. Again, most of these medicines would have been preserved with BAK.

- The basal tear turnover, (normal tear production, excluding reflex tearing), of 20 patients with open-angle glaucoma or ocular hypertension was measured by computerised objective fluorophotometry when using topical timolol preserved with BAK and two weeks after changing to topical preservative-free timolol (Kuppens *et al* 1995). The tear turnover of the patients before the change was 32% lower than that of healthy controls. A mean increase of 28% in the individual tear turnover values was noted after the change to the preservative-free timolol formulation ($p=0.04$).

- The effect of topical timolol with and without BAK on the epithelial permeability (a measure of cell membrane damage) and autofluorescence (a measure of cellular metabolism) of the cornea, was investigated in patients with POAG or ocular hypertension (de Jong *et al* 1994). The corneas of 21 patients were examined during treatment with timolol preserved with BAK at concentrations of 0.25% or 0.5%. After two weeks, patients were switched to treatment with timolol without BAK. Corneal epithelial permeability decreased significantly (mean decrease per patient 27%; $p=0.025$), whereas corneal autofluorescence increased significantly (mean increase per patient 6%; $p=0.003$) when switching to a BAK-free formulation. The authors considered that the results indicated that an improvement in corneal epithelial function occurred following the withdrawal of BAK.

- Numerous reports had also indicated that, even without evident symptoms or clinical manifestations, abnormal signs of inflammation were observed in the conjunctival epithelium of glaucoma patients. Immuno-inflammatory markers and mediators of the conjunctival epithelium of medically treated patients with glaucoma were found to be significantly increased, compared with healthy controls (Baudouin *et al* 2004; Baudouin, Pisella *et al* 2004). The intensity of this inflammatory reaction seemed to be related to the number of antiglaucoma medicines used, and the duration of treatment (Ariturk *et al* 1997).

Alcon submitted that it was clear from the above brief summary that the use of glaucoma medicines preserved with BAK had been associated with signs and symptoms of OSD, decrease in tear turnover rate, increased epithelial cell permeability and an increase in conjunctival inflammatory markers in the clinical situation. Alcon noted that the studies cited only represented a fraction of the information available in the literature relating to this situation. The effects of BAK on corneal and conjunctival epithelial cells in animal and *in vitro* models mirrored the clinical picture described above and had also provided further information concerning the underlying cellular mechanisms involved. As such, they were now used widely as predictive tools in research and data generated from these models was recognised and used by regulatory bodies worldwide.

- Pissela *et al* (2000) found that rabbits given a preserved beta-blocker (Timoptol 0.25% and 0.50%, preserved with 0.01% BAK) displayed a significantly greater reduction in tear film break-up time compared with those given a non-preserved beta-blocker containing the same concentrations of active, whilst Noecker *et al* (2004) found that treatment of rabbits with glaucoma medicines that contained higher levels of BAK resulted in greater damage to the cornea and conjunctiva compared with treatment with preparations preserved with lower concentrations of BAK.

- The effect of different concentrations of BAK (0.1–0.0001%) was studied on a continuous human conjunctival cell line: the Wong–Kilbourne derivative of Chang conjunctiva (De Saint Jean *et al* 1999). Cells were treated for 10 minutes and were assessed before treatment and at 3, 24, 48 and 72 hours after treatment. BAK at concentrations of 0.1% and 0.05% caused immediate cell lysis, while exposure to 0.01% BAK was associated with cell death within 24 hours. Doses of 0.005–0.0001% BAK induced apoptotic cell death at 24-72 hours in a dose-dependent manner.

- Pisella *et al* (2004) compared the toxicities of 0.005% latanoprost preserved with 0.02% BAK, 0.5% timolol preserved with 0.02% BAK, unpreserved 0.5% timolol and 0.02% BAK alone on the Wong–Kilbourne derived human conjunctival cell line. Cells were treated for 15 minutes and subsequently left to recover for 0, 4 and 24 hours in a normal medium. Both latanoprost and timolol were associated with toxic proapoptotic effects on conjunctival cells, whereas no toxic effect was observed with unpreserved timolol. Both medicines were less toxic than BAK alone.

- In another recent study, immortalized human conjunctival and corneal epithelial cells were exposed to BAK (0.001–0.1%) for one hour. It was found that BAK induced significant amounts of interleukin (IL-) 1 and tumour necrosis factor (TNF), but only moderate amounts of C-reactive protein (CRP), IL-10 and IL-12. Lower concentrations of BAK induced proportionally less elaboration (Epstein *et al* 2009).

Again, the above represented a mere sample of the confirmatory studies available in the literature.

In view of the extensive literature relating to the potential toxicity of BAK, and the high cost of treating glaucoma patients long-term with single use, preservative-free preparations, Alcon had developed two formulations of Travatan that were preserved with potentially less toxic preservatives.

Travatan Z, introduced into the US a number of years ago was preserved with sofZia, a proprietary oxidising preservative system. In clinical studies, Travatan Z produced a significant decrease in conjunctival hyperaemia and superficial punctate keratitis (SPK) severity in patients with open-angle glaucoma or ocular hypertension, who had previously been treated with latanoprost preserved with BAK (Aihara *et al* 2011; Yamazaki *et al* 2010). The level of SPK was a measure of corneal epithelial cell damage and the improvement noted was found to be maintained over one year of ongoing therapy (Aihara *et al*). Travatan Z had also been shown to produce a reduction in OSDI scores in problematic patients previously treated with latanoprost preserved with BAK, when used for up to 12 weeks (Katz *et al* 2010) and an improvement in mean OSDI scores in patients previously treated with latanoprost or bimatoprost (both preserved with BAK), who needed alternative therapy due to tolerability issues (Henry *et al* 2008). Finally, in another study, when 20 consecutive patients using latanoprost preserved with BAK were switched to Travatan Z, it was found that tear film break-up time, a measure of tear film instability, increased significantly when evaluated at eight weeks, while mean inferior corneal staining and mean OSDI scores both decreased significantly (Horsley and Kahook 2009).

Alcon submitted that, due to regulatory constraints, Travatan Z was not marketed in Europe but an alternative formulation, preserved with Polyquad, was developed for this market. Polyquad, a polyquarternary preservative, had a long history of safe and effective use in contact lens care and dry eye products in Europe and throughout the rest of the world. The ocular safety of Polyquad had also been compared with BAK in *in vitro* and animal models.

- *In vitro*, Polyquad-containing solutions had no discernible effects on the cytokinetic movement or on mitotic activity of human corneal epithelial cells, while BAK 0.01% caused immediate cell retraction and cessation of normal cytokinesis, cell movement and mitotic activity in the same model (Tripathi *et al* 1992).

- In a rabbit model, designed to evaluate the effect of artificial tear solutions on the corneal epithelial

barrier by measuring the uptake of carboxyfluorescein following exposure to test solutions, exposure to solutions containing 0.01% BAK caused an approximate 10 to 100-fold increase, while solutions preserved with Polyquad caused little or no increase (Lopez Bernal and Ubels 1991).

- More recently, Polyquad and BAK had been compared in an acute rat ocular toxicity model. Compared to Polyquad, BAK consistently and dramatically altered the corneo-conjunctival surface as evaluated by slit-lamp examination, fluorescein staining, impression cytology, in vivo confocal microscopy and histology. Although high concentrations of Polyquad had some effects on goblet cell density and some abnormalities were observed with in vivo confocal microscopy, when compared with an unpreserved balanced salt solution control, Polyquad was generally far less toxic than BAK in this model (Labbe *et al* 2006).

Alcon submitted that in the clinical situation, Polyquad had been used successfully for many years in artificial tears and ocular lubricants designed for long-term use. The potential effects of the preservative on the ocular surface were, however, difficult to evaluate in such products since they were used to ameliorate OSD. However, the low potential for ocular surface toxicity of Polyquad had been confirmed by its use in soft contact lens disinfecting and lubricating solutions. Soft contact lenses could act as a reservoir for preservative molecules on the eye and therefore could exacerbate any toxic effects that might be seen after normal ocular administration of eye drops. In numerous studies, solutions containing Polyquad induced minimal corneal staining in soft contact lens wearers and significantly lower levels of staining than solutions containing other cationic preservatives, such as polyhexanide (Jones *et al* 2002, Pritchard *et al* 2003, Jones *et al* 2005, Andrasko and Kelly 2008). The good ocular tolerance of Polyquad in soft contact lens wearers persisted in the longer-term (Gibbs *et al* 1989).

Alcon submitted that prior to launch of Travatan preserved with Polyquad, it was not feasible or practical to conduct long-term, large scale clinical studies designed to evaluate ocular safety and, given the substantial clinical database supporting the ocular safety of Polyquad, such studies were not necessary for regulatory purposes. However, the effects of Travatan preserved with Polyquad were evaluated in both rabbit and *in vitro* models.

- In the rabbit model, Travatan preserved with Polyquad was compared with phosphate-buffered saline, BAK 0.015% in water, Polyquad 0.001% in water, Travatan preserved with BAK (0.015%) and latanoprost preserved with BAK (0.02%). 50 µL of each solution was instilled 15 times, at 5 minute intervals, in both eyes of the rabbits. Assessments involved clinical observation of the rabbit eyes, *in vivo* confocal microscopy (IVCM), conjunctival impression cytology and immunohistological evaluation. Travatan preserved with Polyquad did not produce obvious irritation by clinical observation, changes in microstructures of the whole ocular surface as measured by *in vivo* confocal microscopy, inflammatory infiltration or cell damage as measured by impression cytology, altered levels of goblet cell counts or significant infiltration of CD45+ cells in the cornea. These findings were similar to those for phosphate-buffered saline and Polyquad 0.001% in water and significantly better than findings for Travatan preserved with BAK, latanoprost preserved with BAK and BAK 0.015% in water (Liang *et al* 2010).

- In an *in vitro* human conjunctival cell model, Travatan preserved with Polyquad was compared with phosphate-buffered saline, BAK 0.015% in water, BAK 0.02% in water, Polyquad 0.001% in water, Travatan preserved with BAK (0.015%) and latanoprost preserved with BAK (0.02%). Cells were incubated with the test compounds (50 µL/well) for 30 minutes at 37ºC with 98% humidity and 5% CO2. Six toxicological assays were used to assess three different cytotoxic responses: cell viability (neutral red, Alamar blue), apoptosis (YO-PRO-1, Hoechst 33342), and oxidative stress (H2DCF-DA, hydroethidine). In addition, the apoptosis and oxidative stress assays were each reported according to cell viability as observed with neutral red and Alamar blue. Travatan preserved with Polyquad demonstrated significantly improved cell viability and significantly less cytotoxicity, apoptosis and oxidative stress than any of the BAK-containing solutions (Brignole-Baudouin *et al* 2010).

- In a second *in vitro* investigation involving cultured human corneal and conjunctival epithelial cells, the effects of Travatan preserved with Polyquad on cell viability were compared with those of Travatan Z, sofZia vehicle, Travatan preserved with BAK, commercially available solutions containing latanoprost and tafluprost (both preserved with BAK) and a range of concentrations of BAK (0.001% to 0.05%). Cells were incubated with 100 µL of each solution for 25 minutes at 37ºC and 5% CO2. The toxicity of the prostaglandin analogues latanoprost, tafluprost and Travatan preserved with BAK was similar to the toxicity observed with their respective BAK concentrations. Travatan preserved with Polyquad and Travatan Z both provided significantly greater corneal and conjunctival cell survival than the BAK-preserved solutions. Travatan preserved with Polyquad demonstrated slightly improved survival of both corneal and conjunctival cells than Travatan Z, although the difference did not reach statistical significance in either case (Ammar *et al* 2010).

In summary Alcon submitted that in response to concerns about the potential effects on the ocular surface of long-term treatment of some patients

with glaucoma medicines preserved with BAK, it had developed two formulations of Travatan preserved with potentially less harmful preservatives, Polyquad and sofZia. The latter formulation was not available in Europe but had been on the US market for a number of years and had been the subject of a number of Phase IV post-marketing clinical studies, in contrast to Travatan preserved with Polyquad which had only recently obtained regulatory approval in Europe.

- The adverse effects of BAK-preserved medicines on the ocular surface had been demonstrated to be reversed, at least in a proportion of patients, when the medicines were replaced by preservative-free products, or, in the case of latanoprost and bimatoprost preserved with BAK, when substituted with Travatan Z, preserved with sofZia.

- The adverse effects of BAK-preserved glaucoma medicines observed in clinical studies had been duplicated in animal and *in vitro* models, which, therefore, provided powerful screening tools for use in the development of new formulations and a useful guide to glaucoma specialists of the likely clinical performance of these formulations. The usefulness and predictive value of such models was widely recognised by regulatory authorities and by ophthalmologists.

- Polyquad had an excellent ocular safety profile when used in soft contact lens care solutions and had been used for many years in artificial tears and ocular lubricants. In animal and *in vitro* models it had been clearly shown to be less toxic to corneal and conjunctival epithelial cells than BAK.

- In animal and *in vitro* models, Travatan preserved with Polyquad had a beneficial ocular safety profile compared with Travatan and latanoprost preserved with BAK and in an *in vitro* model it had at least a similar safety profile to Travatan Z.

With regard to the Panel's rulings, Alcon submitted that the thornless rose visual did not appear in isolation and must be interpreted in association with the accompanying text. The Panel noted that the prominent headline in the top right hand corner was 'Introducing BAK-free formulation Travatan'. In the Panel's view, most readers would associate the picture of the rose with the prominent headline and thus see the rose as representing Travatan without BAK. Alcon agreed with this association and indeed this was the intention of the advertisement. By extension, the thorns around the base of the stem must represent BAK. In its response above, Alcon made it clear that this was the interpretation intended by the association of the visual with the claim 'Introducing BAK-free formulation Travatan'.

Alcon noted that the Panel, however, 'considered that thorns on a rose stem would be seen as something injurious; the advertisement implied that Travatan preserved without BAK was free of such hazard'. Alcon disagreed with this interpretation, it was not the intention of the visual or the advertisement to convey such a message. Thorns on a rose were not generally associated with injury but regarded, at worse, as an inconvenience – something that was unfortunate and unwanted. This association resonated very well with the views of most ophthalmologists about the presence of BAK in glaucoma medicines. The attempt by Allergan and the Panel to associate the visual with the side effect profile of Travatan preserved with Polyquad was therefore flawed. This was particularly so because all glaucoma specialists knew that many of the local ocular side effects of current multidose prostaglandin analogue presentations eg irritation, hyperaemia, change in iris colouration, growth of eyelashes, change in skin pigmentation, were associated with the prostaglandin analogue molecule itself rather than BAK (Camras *et al* 1997). It was well known that the effects of BAK were more subtle and longer-term and were particularly associated with a sub-group of patients who either already had, or had a propensity to develop, OSD. Indeed, studies had indicated that the presence of prostaglandin analogues in a formulation could actually moderate, although not eliminate, some of the effects of BAK, which, in any event, were known to be dose dependent (Pisella *et al* 2004).

However, Alcon submitted that even in the unlikely event that a glaucoma specialist associated the thorns in the visual with the side effect profile of Travatan, the comparison attempted by the Panel would still be flawed.

The Panel noted that, 'Section 4.8, Undesirable effects, of that SPC [for Travatan preserved with Polyquad] still listed punctate keratitis as a common (>1/100 to <1/10) side effect of therapy. The Panel thus noted that Travatan preserved with Polyquad was still associated with one of the ocular side-effects referred to in Section 4.4 of the SPC for Travatan preserved with BAK. Further, Section 4.8 of the SPC for Travatan preserved with Polyquad listed another ten possible ocular adverse events which were also listed as possible adverse events in the SPC for Travatan preserved with BAK. In this regard the Panel did not consider that the thornless rose was a fair reflection of the side effect profile of Travatan preserved with Polyquad compared with Travatan preserved with BAK'.

Alcon submitted that it was widely recognised within the medical community that the comparative safety of two medicines could not be determined from information contained in their SPCs alone, particularly when one product had been marketed for a number of years and the other only recently introduced. Such comparisons could only be made as a result of appropriately designed and powered comparative clinical studies. The Panel knew that Travatan preserved with Polyquad was introduced as a result of a variation to Alcon's existing marketing authorization. Given that the change related to the replacement of one widely used

ophthalmic preservative with another, the regulatory focus for this variation was clinical efficacy and preservative efficacy. The long-term, large scale safety clinical studies required for registration of a new product were therefore not required in this case and the SPC for Travatan preserved with Polyquad, at this stage must clearly be expected to reflect this fact, and to build on the existing SPC, by any reasonable assessment. Alcon was therefore unclear why the Panel had tried to base its judgement solely on an SPC comparison in this case. It seemed highly unlikely that the visual in question, when viewed in the context of the advertisement, would seriously mislead a glaucoma specialist about the ocular safety profile of Travatan preserved with Polyquad as alleged. Alcon noted that the prescribing information for the product, which gave the appropriate details of the side effect profile, appeared at the bottom of the advertisement.

Alcon submitted that since it had established, and as agreed by the Panel, that the thorns in the visual represented BAK, the only comparison that could realistically be considered to be implied related not to the safety profile of the product but to the ocular safety profiles of BAK and Polyquad, when used in the concentrations necessary for appropriate preservative activity. This comparison was well established in the literature, as explained above, and was alluded to in the advertisement. The visual could, therefore, not be considered to mislead in this regard. However, Alcon noted that even this comparison was not the intention of the visual. As previously explained, the visual, in association with the words, 'Introducing BAK-free formulation Travatan', was simply intended to illustrate the complete removal of the 'unwanted' BAK from Travatan.

Alcon denied that breaches of Clauses 7.2, 7.3 and 7.10 since any comparison conveyed by the visual, in the context of the advertisement, was fair, accurate, capable of substantiation, not exaggerated and could not be considered to mislead the target audience, either directly or by implication.

COMMENTS FROM ALLERGAN

Allergan stated that this case did not relate to and nor did it take issue with the wealth of literature about the safety and efficacy profile of BAK. Indeed, Allergan understood the side effect profile of this preservative very well and was well aware of the precautions restricting use in certain patient groups, such as those with OSD. The crux of the complaint was about the lack of clinical evidence to support claims of an improved safety profile for Travatan preserved with Polyquad compared with Travatan preserved with BAK. Allergan did not consider that any such tolerability benefits had been demonstrated in clinical studies conducted by Alcon and therefore claims for an improved safety profile should not be made until proven in clinical studies.

Allergan considered that reference to Travatan Z (preserved with sofZia) introduced in the US and unavailable in the UK, was irrelevant.

Allergan did not consider the claims for Polyquad compared with BAK in *in vitro* and animal studies to be at issue here. However, Allergan strongly contested the application of these laboratory studies to demonstrate a clinical benefit in terms of tolerability for patients since it was not aware of any clinical studies to demonstrate this. Indeed, the only one clinical study which compared travoprost preserved with Polyquad and travoprost preserved with BAK showed that the safety profile was similar for both products (Denis *et al* 2010). The authors concluded that 'the safety profile of travoprost BAK free was similar to that of travoprost BAK'. The SPC for this new formulation also listed eye irritation, dry eye, pruritus, eye pain and ocular discomfort as common undesirable effects. Alcon had not supplied any additional clinical data comparing travoprost preserved with Polyquad and travoprost preserved with BAK to support its assertion of an improved safety profile within its advertisements.

Allergan alleged that it was disingenuous of Alcon to maintain that the rose visual was not intended to represent the tolerability profile of travoprost preserved with Polyquad. However, even if the line of argument was followed that the visual was intended to represent an absence of BAK, this in itself was misleading since the product was not preservative-free. Polyquad had not been used previously in treatments for glaucoma and as yet the tolerability profile of such treatments had not been established in large scale clinical studies.

Allergan considered Alcon's comments about the side effect profile listed in the SPC for travoprost preserved with Polyquad were fundamentally flawed. Promotion of a medicine must be in accordance with the terms of its marketing authorization and not be inconsistent with the particulars listed in its SPC. The side effects listed on the SPC for travoprost preserved with BAK must of course remain on the SPC until evidence from large scale clinical studies demonstrated an improved safety profile for travoprost preserved with Polyquad, which would permit their removal. However, Denis *et al* demonstrated a similar number of ocular adverse events for both travoprost preserved with Polyquad (n=185) and travoprost preserved with BAK (n=186); dry eye 5 (2.7%), 3 (1.6%), eye irritation 6 (3.2%), 9 (4.8%) and eye pruritus 7 (3.8%), 6 (3.2%) respectively.

Allergan agreed with Alcon that comparisons of the side effect profiles of two products could only be made via appropriately designed and powered clinical studies. Currently, there was no such evidence. Allergan alleged that Alcon's defence that because there was no further data from such studies for travoprost preserved with Polyquad, there were *de facto*, no such side effects, was fundamentally flawed and incorrect. Allergan agreed with the Panel's ruling on this matter and considered it appropriate that the Panel had ruled

on this matter based on the approved SPC for the product.

Allergan therefore agreed with the Panel's ruling that the thornless rose visual was not a fair reflection of the side effect profile of travatan preserved with Polyquad in breach of Clauses 7.2, 7.3 and 7.10.

APPEAL BOARD RULING

The Appeal Board considered that most people would view the thorns on a rose as injurious. The thornless rose in the context of the headline 'Introducing BAK-free formulation Travatan' implied that BAK-free Travatan was better tolerated than that preserved with BAK. However, the Appeal Board noted that the only direct clinical comparison of Travatan preserved with Polyquad and Travatan preserved with BAK (Denis *et al*) concluded that the safety profiles of the two were similar. The Appeal Board considered that the visual was misleading and exaggerated the difference between the two formulations of Travatan as alleged. The Appeal Board upheld the Panel's ruling of a breach of Clauses 7.2, 7.3 and 7.10. The appeal on this point was unsuccessful.

2 Advertisement – Implied claim for 'preservative free' and claim regarding side-effect profile

COMPLAINT

Allergan alleged that the claim 'Travatan BAK-free', used to alert customers to the newly formulated Travatan, misled as it implied that the product was preservative-free, when in fact it was preserved with Polyquad. This preservative was clearly not 'side-effect free' as was generally implied in the advertisement and with the campaign visual. Allergan also considered the use of laboratory studies within the advertisement was unacceptable to support general claims regarding tolerability. Allergan was not aware of any clinical data to support the tolerability claims made in the advertisement for Polyquad when compared with BAK.

Allergan noted that Denis *et al* demonstrated a similar number of ocular adverse events for both Travatan preserved with Polyquad and Travatan preserved with BAK; dry eye 5 (2.7%) and 3 (1.6%), eye irritation 6 (3.2%) and 9 (4.8%) and eye pruritus 7 (3.8%) and 6 (3.2%) respectively.

The claims were therefore misleading in breach of Clauses 7.2, 7.3 and 7.10. In inter-company dialogue, Alcon considered the information that it presented regarding laboratory studies to be permissible and that extrapolation of findings relating to the relative behaviour of Travatan in these models was of direct relevance and clinical significance. Allergan disagreed since it was generally established that laboratory studies which showed significant differences between products did not necessarily translate into clinical differences in patients. In this instance, this was indeed the case as Denis *et al* demonstrated a similar level of ocular adverse events for Travatan preserved with Polyquad and Travatan preserved with BAK.

Allergan was concerned that clinicians would take away from this campaign that Travatan (preserved with Polyquad) was a preservative-free product and that it had an improved safety profile vs the previous formulation preserved with BAK; both messages were incorrect and misleading. Allergan believed this had been a deliberate campaign to mislead clinicians as to the safety profile of Travatan preserved with Polyquad. Due to the serious nature of its concerns, and the fact that the misleading visual related to the safety profile for Travatan and might prejudice patient safety, Allergan also alleged that the campaign visual breached Clause 9.1.

RESPONSE

Alcon found Allergan's suggestion that BAK-free implied that the Travatan was preservative-free difficult to understand. There was an asterisk immediately after the first use of the term that drew attention to a footnote that made it clear that BAK related to benzalkonium chloride. Further, the statement in the advertisement immediately following the heading in large, clear, bold text was: 'A multidose prostaglandin analogue with POLYQUAD'. Alcon noted that Polyquad was an already established preservative which had been used in ophthalmic preparations, such as contact lens solutions for around 20 years and so was well known by ophthalmologists. Therefore, the claim did not imply that the product was preservative-free, only that it did not contain BAK as the preservative. This was an important and relevant claim to make as there were well documented advantages to removing BAK from ocular medicines. The benefits of Travatan BAK-free had been demonstrated in laboratory studies which showed the benefits of using Polyquad over BAK and these benefits were further substantiated by the removal from the SPC of the special warning in Section 4.4. Alcon therefore could not accept that BAK-free, as it appeared in the advertisement, could possibly be misinterpreted by the expert audience to whom it was addressed, and the statement was not misleading.

The assertion from Allergan that the rose without thorns suggested Travatan was 'side-effect free' was nonsensical. Rather, Alcon had stated that Polyquad had been shown to be 'gentler' and 'less toxic', not that the new Travatan formulation did not have any side-effects. These claims had been made in text which was clear, placed in an obvious position and in an appropriately large font. Therefore, it was hard to believe that the intended audience within the ophthalmic field (who were already highly knowledgeable about glaucoma medicines) could be misled in this way, particularly in light of the surrounding text, but also considering that both the prescribing information and SPC for the product

were readily available to them. As explained above, Alcon had not implied that overall Travatan had an improved ocular safety profile, either by reference to Denis *et al* (a non-inferiority study), or in any other way.

Alcon believed that the extrapolation of laboratory data to the clinical situation was permissible in this instance. It was made clear in the advertisement that the data was derived from 'laboratory studies' (second bullet point) and '*in vitro*' studies (third bullet point). The non-clinical data that was referenced with regard to the BAK-free formulation of Travatan was based on well established *in vivo* animal models and *in vitro* models which used cultured human conjunctival epithelial cells that were sufficiently robust to be included in the variation to the marketing authorization for the reformulation of Travatan, assessed by the European Medicines Agency (EMA). Indeed, the use of laboratory data derived from well established models was commonplace in this field. Allergan would be well aware of this considering that, to support the registration of its product Lumigan, it had conducted six pharmacokinetic laboratory studies in rabbits (both *in vitro* and *in vivo*). These studies were accepted by the Committee for Medicinal Products for Human Use (CHMP) and were cited in the European Public Assessment Report (EPAR) for Lumigan (EMA/105752/2010). In the circumstances described above, and considering that laboratory data derived from well established models had been consistently acceptable for the CHMP/EMA in this field, it was appropriate to extrapolate the findings of the studies cited in the advertisement (based on well established models) to support the general claims in the promotional campaign. Alcon further noted in the Lumigan EPAR that, due to the cytotoxic properties of BAK 'it is, from a safety point of view, preferable to minimise its presence in ophthalmic preparations' and, in this context, Allergan submitted preliminary results from a newly conducted ocular absorption study in rabbits in response to the CHMP's request to substantiate why similar efficacy could not be obtained with a formulation containing a lower BAK concentration.

Alcon referred to Allergan's asserted that clinicians would take away from the campaign two incorrect and misleading messages ie that Travatan was preservative-free and had an improved safety profile vs the previous formulation preserved with BAK. Alcon maintained that the advertisement was compliant with the Code, including Clauses 7.2, 7.3, 7.10 and 9.1, as explained below.

- Alcon had not implied that the new formulation was preservative-free; rather, it had specifically stated that the new formulation was 'with POLYQUAD', a well-known preservative. Further, that the new formulation was 'BAK-free' was an accurate and relevant statement which was important to highlight to ophthalmologists. Stating that Travatan was BAK-free, and illustrating this with the rose without thorns image did not imply that the new formulation was side-effect free.

- In relation to the campaign visual, the advertisement could not be considered to be a misleading comparison between Alcon's product and a competitor's product; the image unambiguously compared the original formulation of Travatan and the new BAK-free formulation – nothing more. The feature compared between the two formulations of Travatan (namely the presence/absence of BAK) was material, relevant and not misleading.

- The presentation of the new Travatan formulation was objective, tempered and did not compromise rational use of the medicine. The rose without thorns image was unambiguous in light of the accompanying text which explained that laboratory and *in vitro* studies had demonstrated that Polyquad was 'gentler' and 'less toxic' compared with BAK. The advertisement did not imply that Travatan (BAK-free) had some special merit, quality or property which had not been substantiated; the advantages of removing BAK were well-known.

Finally, Alcon strongly refuted that it had engaged in a deliberate campaign to mislead clinicians as to the safety profile of the new formulation of Travatan. This allegation was unfair and unsubstantiated. Those within the ophthalmic field would not be misled into believing that the removal of BAK equated to an absence of all side-effects or an improved safety profile overall. Further, ophthalmologists would understand why the known ocular irritant, BAK, was likened to thorns. Alcon could not accept that the advertisement (or indeed the campaign more generally) might prejudice patient safety; this statement was alarmist and unjustified. In these circumstances, Alcon believed that it had not compromised high standards in breach of Clause 9.1.

PANEL RULING

The Panel did not consider that the claims that Travatan was BAK-free implied that it was also preservative-free. The advertisement clearly referred to 'A multidose prostaglandin analogue with POLYQUAD'. In the Panel's view, readers of the British Journal of Ophthalmology would be familiar with Polyquad as a preservative and never expect a multidose presentation to be preservative-free. The Panel did not consider that the claims were misleading as alleged. No breach of Clause 7.2 was ruled.

The Panel noted that the advertisement included, *inter alia*, the claim 'Contains Polyquad, which had demonstrated a gentler effect on the ocular surface than BAK in laboratory studies'. The studies cited in support of this claim (Labbé *et al* 2006 and Liang *et al* 2010) compared the ocular surface toxicity of BAK and Polyquad in rats and rabbits respectively. Both studies reported that Polyquad was less toxic than

BAK but both groups noted that ophthalmic medicines were intended for long-term treatment and as the studies had taken place over a short time period, the long-term safety of Polyquad had not been examined. Nonetheless, Polyquad might be a suitable replacement for BAK.

The advertisement also included the claim 'Significantly less toxic to human conjunctive and coneal epithlial cells when compared to latanoprost solutions (preserved with 0.02% BAK *in vitro*)'. This claim was referenced to Brignole-Baudouin *et al* (2010) which assessed the cytotoxicity on isolated human conjunctival epithelial cells of Travatan preserved with Polyquad vs Travatan preserved with BAK. The authors concluded that their results supported the safety of BAK-free Travatan and that, by implication formulations preserved with Polyquad might be better for ocular surface health than solutions containing BAK.

The Panel noted that the supplementary information to Clause 7.2 stated that care must be taken with, *inter alia*, *in vitro* or animal studies so as not to mislead with regard to their significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance. In contrast to the animal and *in vitro* studies cited above, Denis *et al* was a 3 month double-blind, randomized, parallel group, non-inferiority clinical study to compare the efficacy of Travatan preserved with BAK vs Travatan preserved with Polyquad. The authors reported that no clinically relevant differences in the adverse event profile of the two formulations were identified.

The Panel considered that the animal and *in vitro* studies cited in the advertisement implied that BAK-free Travatan had a better safety profile compared with Travatan preserved with BAK. The only direct clinical comparison of the two (Denis *et al*) did not show that to be the case. The Panel considered that the advertisement was misleading and exaggerated in that regard. A breach of Clauses 7.2, 7.3 and 7.10 was ruled.

The Panel noted its rulings above and considered that high standards had not been maintained. A breach of Clause 9.1 was ruled.

APPEAL BY ALCON

Alcon submitted that the claims in the advertisement citing animal and *in vitro* studies were factual, clear and unambiguous and every attempt was made to ensure that they could not be misinterpreted and that they did not mislead, either directly or by implication.

The claims noted by the Panel were, 'Contains Polyquad, which has demonstrated a gentler effect on the ocular surface than BAK in laboratory studies,' and, 'Significantly less toxic to human conjunctival and corneal epithlial cells when compared to latanoprost solution (preserved with 0.02% BAK *in vitro*)'. Alcon submitted that both claims were suitably referenced statements of fact, which did not mislead or misrepresent. However, the Panel, 'noted that the supplementary information to Clause 7.2 stated that care must be taken with, *inter alia*, *in vitro* or animal studies so as not to mislead with regard to their significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance'. In contrast to the animal and *in vitro* studies cited above, Denis *et al* was a three month, double-blind, randomized, parallel group, non-inferiority clinical study to compare the efficacy of Travatan preserved with BAK with that of Travatan preserved with Polyquad. The authors reported that 'no clinically relevant differences in the adverse event profile of the two formulations were identified'.

Alcon submitted that it had taken the supplementary information to Clause 7.2 into account when preparing the advertisement. With regard to the Panel's rulings, Alcon observed that:

- The claims at issue did not directly extrapolate the animal and *in vitro* data presented to the clinical situation. This extrapolation had been implied by the Panel although this was not unreasonable given the very strong association established in the literature between the results of animal and *in vitro* data, of the type presented, and the clinical situation with regard to treatment of glaucoma.

- Denis *et al* was a regulatory study designed to demonstrate non-inferiority in terms of IOP-reducing efficacy of Travatan preserved with Polyquad, when compared with Travatan preserved with BAK. It was of only three months' duration and included a number and profile of subjects appropriate for its intended objective. The study also did not include the specialised testing needed to detect differences relating to the known long-term effects of BAK, such as measurement of tear film break-up time, OSDI type questionnaires, impression cytology etc. The study was therefore not intended to or designed to detect long-term differences in the effects of the two formulations on ocular surface health. Such studies could take many years to complete and were almost certain to be Type IV post-marketing studies. It was therefore unreasonable to expect such studies to have been conducted at the time of product launch. As such, the Panel's conclusions, based solely on Denis *et al*, were invalid.

- A very strong correlation had been established in the literature between the type of animal and *in vitro* data cited in the advertisement for Polyquad and Travatan preserved with Polyquad and the observations relating to the treatment of glaucoma as made clear by the summary of data presented above. In Alcon's view, therefore, there was a clear rationale to confirm that the animal and *in vitro* data cited was of direct relevance

and significance to the clinical situation. The advertisement, however, did not overstate or exaggerate this relevance and significance and therefore did not mislead.

Alcon noted that Clause 7.2 stated that, 'Material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine'. Given the strong association between animal and *in vitro* data relating to the effects of glaucoma medicines on the ocular surface and the effects observed in clinical practice, withholding information about the known ocular safety profile of Polyquad and Travatan preserved with Polyquad, obtained from animal and *in vitro* studies, simply because confirmatory long-term clinical studies had not been conducted, would have contravened Clause 7.2. It was therefore puzzling that in its rulings, the Panel appeared to endorse such a course of action.

Alcon denied breaches of Clauses 7.2, 7.3 and 7.10 since the reference to animal and *in vitro* data did not attempt to mislead with regard to their relevance or significance, nor did it directly attempt to extrapolate the data to the clinical situation. In any event, there was data to show that the animal and *in vitro* data cited was of direct relevance and significance to the clinical situation and withholding the information, which would help a clinician to form an opinion of the therapeutic value of the medicine, could be considered to be a breach of Clause 7.2. By providing this information, but making the source very clear, Alcon enabled the clinician to judge its relevance based on his own expert opinion and experience.

Alcon noted that Allergan stated that, due to the serious nature of its concerns, and the fact that this misleading visual related to the safely profile for Travatan and might prejudice patient safety, the campaign visual breached Clause 9.1. The alleged breach of Clause 9.1 thus related to the visual only, and not to the advertisement as a whole, and also implied that its use could prejudice patient safety. Since there was no convincing data to clearly prove either an efficacy or safety disadvantage for patients using Travatan preserved with Polyquad, compared to other medical treatments for glaucoma, Alcon concluded that Allergan's allegation was exaggerated and unsubstantiated. Since the Panel did not refer to this part of Allergan's complaint, Alcon assumed that it did not agree with it.

Alcon submitted that the ruling of a breach of Clause 9.1 therefore rested solely on the previous rulings of breaches in Clauses 7.2, 7.3 and 7.10. Since Alcon had demonstrated above that no breaches of those clauses had taken place, it followed that there had also been no breach of Clause 9.1. Given the nature of the regulatory process required and the data that needed to be generated to introduce the reformulated version of Travatan, combined with the need to comply fully with the requirements of Clause 7.2 of the Code, it was clear that the highest standards had been maintained at all times. Even in the event of a ruling of any breach of Clauses 7.2, 7.3 and 7.10, Alcon submitted that this would be a technicality resulting from an unintentional misunderstanding and that a finding of a breach of Clause 9.1 was therefore inappropriate.

COMMENTS FROM ALLERGAN

Allergan alleged that the animal and *in vitro* studies cited in the advertisement implied that BAK-free Travatan had a better safety profile compared with Travatan preserved with BAK, while the only direct clinical comparison of the two (Denis *et al*) did not show that to be the case. The advertisement was therefore misleading and exaggerated in that regard in breach of Clauses 7.2, 7.3 and 7.10.

Allergan alleged that the presentation of the claims for Polyquad compared with BAK in *in vitro* and animal studies to be the fundamental issue of this complaint. Allergan was concerned about the use of these studies to support claims for an improved safety profile for travoprost preserved with Polyquad. This was particularly pertinent when considering Denis *et al*. Whilst Allergan accepted that this study was for registration purposes only and designed to show non-inferiority in terms of efficacy, it was still the only clinical study to compare travoprost preserved with Polyquad and travoprost preserved with BAK. Allergan also understood that this study was not designed to detect any differences relating to the specific effects of Polyquad or BAK. However, this was the only clinical data available and it did not support the claims made for an improved ocular safety profile for travoprost preserved with Polyquad compared with travoprost preserved with BAK.

Allergan agreed that material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine. However, Allergan disputed that Alcon had provided sufficient information to enable the recipient to do this by incorrectly presenting data from laboratory studies to support clinical claims for ocular tolerability. Alcon maintained that the information that it presented regarding laboratory studies was permissible and that there was a rationale for information from these models to be presented because it was of direct relevance and clinical significance. Allergan did not consider this to be the case since it was generally established that laboratory studies showing differences between products did not necessarily translate into clinical differences in patients.

Allergan therefore agreed with the Panel's ruling that the presentation of animal and *in vitro* data in this advertisement was misleading and exaggerated in breach of Clauses 7.2, 7.3 and 7.10.

Allergan alleged that this advertisement was misleading as it implied a safety benefit for the product that could not be substantiated and thus might prejudice patient safety. Alcon stated in its

response that since there was no convincing data to clearly prove either an efficacy or safety disadvantage for patients using Travatan preserved with Polyquad compared with other treatments, Allergan's concerns were exaggerated and unsubstantiated. However, Allergan took the opposing view that there was no convincing data to prove either an efficacy or safety advantage for patients using travoprost preserved with Polyquad compared with other treatments and therefore no such safety benefit claims could be supported.

Allergan agreed with the Panel's ruling that high standards had therefore not been maintained and hence there had been a breach of Clause 9.1.

In summary, Allergan was concerned that recipients of this material would be misled as to the significance of the ocular safety data implied by the thornless rose visual. The core issue of Allergan's concerns was that there was an implied clinical benefit for travoprost preserved with Polyquad with no supporting clinical data.

APPEAL BOARD RULING

The Appeal Board noted that under the heading 'Travatan BAK-free formulation:' the advertisement featured two bullet points which referred to animal and *in vitro* studies. In particular the claim 'Significantly less toxic to human conjunctive and corneal epithelial cells when compared to latanoprost solutions (preserved with 0.02% BAK *in vitro*)' was referenced to Brignole-Baudouin *et al* which compared the effects of Travatan BAK-free with travoprost and lantaprost which were both preserved with BAK on isolated human conjunctival epithelial cells. The Appeal Board noted that the authors stated that '…formulations preserved with Polyquad *might* be better for ocular surface health than solutions containing BAK' (emphasis added). In the Appeal Board's view 'Significantly less toxic…' as used in the advertisement was quite different to '…might be better…', as used by Brignole-Baudouin *et al*. The Appeal Board considered that in that regard the claim did not reflect the cited paper.

The Appeal Board considered that although the results of *in vitro* models might predict future clinical effects there was no guarantee that this would be so. When presenting animal and *in vitro* studies care was needed to ensure that, in the absence of clinical evidence, clinical effects were not inferred or claimed. The Appeal Board noted, as in point 1, that the only clinical evidence available (Denis *et al*) concluded that the safety profile of Travatan preserved with Polyquad was similar to that preserved with BAK.

The Appeal Board considered that the *in vitro* and animal data presented in the advertisement implied that BAK-free Travatan was better tolerated than that preserved with BAK and this was not supported by the available clinical data. The Appeal Board considered that the advertisement was misleading and exaggerated in that regard. The Appeal Board upheld the Panel's ruling of a breach of Clauses 7.2, 7.3 and 7.10. The appeal on this point was unsuccessful.

The Appeal Board noted its rulings above and considered that high standards had not been maintained. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

Complaint received **21 February 2011**

Case completed **9 June 2011**