CASE AUTH/2372/11/10

FORMER EMPLOYEE v ALCON LABORATORIES

Promotion of Travatan

A former employee complained that Alcon Laboratories had promoted a formulation of Travatan (travoprost) that was not preserved with benzalkonium chloride (BAK) before the marketing authorization for that formulation had been granted. [The reformulated eye drops were preserved with Polyquad]. Travatan was indicated for the management of ocular hypertension or open-angle glaucoma.

The complainant had emails which showed her manager had asked her to visit all customers after a speaker meeting to 'discuss the potential of BAK-free'. She believed that a competitor company had contacted Alcon and that Alcon had denied all allegations. Five days later, her manager and the other two regional managers telephoned some representatives, not all, to ask them not to discuss BAK-free Travatan. The complainant's call notes and those of a number of other representatives showed that they had discussed this on every available opportunity. The complainant alleged a breach of Clause 2.

An email provided by the complainant referred to an enquiry from a formulary pharmacist to a representative about Polyquad and the response from Alcon referred to slides on Polyquad and listed its properties. The complainant stated that the email, from the Travatan brand manager, was to help representatives to understand what Polyquad was and how the representatives could sell it to their customers.

Another email, from her manager referred to the need to build on the endorsement of Azarga by the speaker at a meeting, his attempt to limit Lumigan use, and the potential of BAK-free. A 1:1 follow-up was stated to be crucial within ten days of the event.

The detailed response from Alcon Laboratories is given below.

The Panel noted that when it received the complaint Travatan preserved with Polyquad was still the subject of a product licence variation. The formulation for which Alcon held a licence at that time was Travatan preserved with BAK. At a meeting held on 30 September/1 October, representatives were briefed on the revised formulation. They were instructed that if ophthalmologists asked them about BAK-free Travatan they were to 'Explain that Alcon will introduce (within the new year) NEW Travatan BAK FREE soon, and explain that the new formulation has proven to be as powerful as the existing Travatan but with a better tolerability profile'. The Panel noted that this instruction went beyond Alcon's submission to the Authority that representatives could simply inform customers of the regulatory status of BAK-free Travatan if asked.

The Panel noted that as a result of this complaint, Alcon emailed its representatives on 24 November and asked them to ensure that there were absolutely no conversations about Travatan BAK-free until it had a product licence. An analysis of the call records showed that one representative in particular regularly referred to BAK-free Travatan from early October until early November. A typical entry by that individual read 'Briefly mentioned Travatan in terms of absolute IOP [intra-ocular pressure] drop, control of diurnal fluctuations, tolerability, price and future BAK free formulation'. It appeared from the call notes that any discussion about BAK-free Travatan had been initiated by the representative and not a health professional. In that regard the Panel noted Alcon's submission that the content of call notes was often not scrutinised in detail and that any indication that a representative had not adhered to company policy might not be picked up at the time unless the practice was widespread. The Panel was concerned about the company's approach which it considered was unacceptable.

The Panel noted that Alcon's product, Systane (a device), was an ocular lubricant preserved with Polyquad and could be promoted. Representatives were instructed to reinforce the message that Systane did not contain BAK, that BAK was associated with ocular surface toxicity and that Polyquad did not exhibit the same ocular surface toxicity as BAK. Representatives were also encouraged to use the promotion of Systane to raise the subject of dry eye in glaucoma patients and its potential link to the presence of BAK in eye drops used for treatment and to assess the level of interest in this topic to assist targeting of future sales activity. In the Panel's view it was likely that the discussion of Systane and problems of dry eye in glaucoma would solicit questions about BAK-free treatments for the condition.

The Panel considered that, on the balance of probabilities, Alcon representatives had promoted BAK-free Travatan before the grant of a marketing authorization which permitted the sale or supply of that formulation. A breach of the Code was ruled.

The Panel further considered that the presentation used to brief the representatives in September/October, which encouraged them to discuss and make claims for Travatan BAK-free, advocated a course of action which was likely to lead to a breach of the Code. A breach of the Code was ruled.

The Panel considered that high standards had not

been maintained. A breach was ruled. The Panel, however, did not consider that the activity was such as to bring discredit upon the industry and no breach of Clause 2 was ruled.

A former employee complained that Alcon Laboratories U.K. Limited had promoted a formulation of Travatan (travoprost) that was not preserved with benzalkonium chloride (BAK) before a marketing authorization for that formulation had been granted. [The reformulated eye drops were preserved with Polyquad]. Travatan was indicated for the management of ocular hypertension or open-angle glaucoma.

COMPLAINT

The complainant alleged that Alcon had actively promoted BAK-free Travatan. She believed this was yet to gain a licence in the UK. She had emails which showed her manager had asked her to visit all customers after a speaker meeting to 'discuss the potential of BAK-free'. She believed that a competitor company had contacted Alcon and that Alcon had denied all allegations. Five days later, her manager and the other two regional managers telephoned some representatives, not all, to ask them not to discuss BAK-free Travatan. The complainant's call notes and those of a number of other representatives showed that they had discussed this on every available opportunity. The complainant alleged a breach of Clause 2 of the Code.

An email provided by the complainant referred to an enquiry from a formulary pharmacist to a representative about Polyquad and the response from Alcon referred to slides on Polyquad and listed its properties. The complainant stated that the email, from the marketing department, was to help representatives to understand what Polyquad was and how the representatives could sell it to their customers.

Another email from her manager referred to the need to build on the endorsement of Azarga by the speaker at a meeting, his attempt to limit Lumigan use, and the potential of BAK-free. A 1:1 follow-up was stated to be crucial within ten days of the event.

The complainant stated that after she had left Alcon, former colleagues had told her that the representatives had been asked by email to no longer promote BAK-free as there had been a complaint from the ABPI.

When writing to Alcon, the Authority asked it to respond in relation to Clauses 3.1, 9.1 and 15.9 in addition to Clause 2 cited by the complainant.

RESPONSE

Alcon noted that, from the documents presented, the complaint appeared to relate to promotional activity that took place between the beginning of October and 24 November 2010, the date that the Authority received the complaint.

The medicine at issue was 'Travatan BAK-free'. No such medicine existed or would exist in the future. Alcon had held a marketing authorization for Travatan since November 2010 and had recently reformulated it to replace the existing preservative, benzalkonium chloride (BAK), with polyquarternium-1 (Polyquad). Alcon obtained approval from the EMEA to market the reformulated product on 29 November 2010 and would commence marketing activities early in 2011. This was not the introduction of a new product but simply the reformulation of an existing one. The new formulation would replace the original formulation and apart from a short transition period, the two formulations would not co-exist.

Alcon had known that approval for the revised formulation was imminent for a number of months and had prepared internally for the change. To this end, the sales force was briefed at a meeting held between 30 September and 1 October 2010 to outline Alcon's sales and marketing strategy. The representatives had to be briefed then because Alcon expected to obtain the approval for the new formulation before the next scheduled meeting in January 2011 and with the intervening Christmas holiday period, it was clear that time for any interim launch meeting would be limited. A copy of the slides used in this briefing was provided. The representatives were not given a copy of the slides, nor were they given any other training or promotional material about the new formulation. It was the misrepresentation of the strategy outlined at this sales meeting, either deliberately or unintentionally, that formed the basis of this complaint.

Alcon explained that it had been known for some time that BAK was toxic to mammalian cells and that the repeated use of eye drops containing it could produce signs and symptoms of ocular surface disease such as dry eye and conjunctival inflammation. BAK was the preservative used in most eye drops marketed in the UK. Most eye drops were for short-term use only and so significant problems relating to the preservative were not encountered. However, in chronic, incurable ophthalmic conditions, such as dry eye and glaucoma, it was now recognised that the repeated exposure to BAK represented a significant clinical issue in certain patients. In some dry eye patients their condition might be worsened by treatment, a condition recognised by the diagnostic term 'ophthalmia medicamentosa'. It had also been documented that glaucoma patients might develop dry eye and/or other ocular surface disease once they started to use eye drops and that their signs and symptoms could be directly related to the number of different BAK-containing eye drops that they used. These issues had been the subject of numerous publications and had been extensively reviewed at international ophthalmic congresses and meetings.

In recent years there had thus been increased interest in the development of ophthalmic products for use by dry eye and/or glaucoma patients that did not contain BAK. This was evidenced by the introduction of many

new unpreserved, single use ocular lubricant products onto the UK market. Multidose ocular lubricants containing alternative, less toxic preservatives had also been introduced, such as Alcon's own product Systane which was preserved with Polyquad. Polyquad had been used for many years in contact lens care products and had been repeatedly shown, *in vitro* and *in vivo*, to be less toxic to ocular tissue than BAK.

With regard to anti-glaucoma products, unpreserved, single use presentations had become available and interest in the issues surrounding BAK within the ophthalmic community had reached unprecedented levels. Alcon noted that the specialist ophthalmic community in the UK was relatively small and very well informed. It would therefore be very difficult to find a UK ophthalmologist who was not aware of recent research relating to the effects of BAK and the efforts to formulate products without it.

The UK ophthalmic community knew that Alcon planned to introduce a variant Travatan formulation that did not contain BAK, for two main reasons:

1 Alcon had marketed a Travatan BAK-free variant in the US since October 2006 (Travatan Z). Travatan Z did not contain Polyquad but was preserved with an alternative proprietary preservative system called sofZia and had been the subject of numerous published papers. In addition, it had been promoted in many of the international ophthalmology journals which although published in the US, and had the majority of their circulation there, represented an important information resource for UK ophthalmologists.

2 Scientific posters and presentations detailing research studies conducted on a formulation of travoprost (the active ingredient in Travatan) preserved with Polyquad were presented at the 9th European Glaucoma Society Congress held in Madrid in 2010.

As the first multidose prostaglandin analogue to be available without BAK, interest in Travatan Z amongst UK glaucoma specialists had been particularly marked. Alcon noted that the cost of currently available unpreserved, single-dose anti-glaucoma eye drops was approximately 39% to 200% more than similar multidose therapy and therefore the introduction of more reasonably priced alternatives was eagerly awaited, as it had significant budgetary implications.

Alcon's representatives called almost exclusively on ophthalmologists who were specialists in glaucoma, all of whom were well acquainted with the facts outlined above. As a result, Alcon's representatives had frequently been asked about availability of a BAK-free formulation of travoprost even though they had always been instructed not to initiate such a discussion.

Alcon addressed each allegation separately.

'Alcon had actively promoted BAK-free Travatan' (presumably meaning the new Travatan formulation, preserved with Polyquad), which 'was yet to gain a license in the UK'.

Alcon submitted that this allegation was untrue and unfounded. As stated above it had informed the sales force about the intended reformulation of Travatan and had provided it with a detailed briefing about the sales and marketing strategy to be adopted once approval of the formulation was obtained. However, representatives had not been instructed to detail the new formulation and had been given no support material to enable them to do so.

At the sales meeting referred to above, Alcon's representatives were instructed that four products would remain on detail for each call for the final quarter of 2010 ie Travatan, Systane, Azarga and Duotrav. Three of these, Travatan, Azarga and Duotrav, were anti-glaucoma products and Systane, as noted above, was an ocular lubricant preserved with Polyquad. For Travatan, the instructions for the cycle were to reinforce Alcon's competitive position with regards to efficacy and safety, in preparation for the increased marketing activity that would take place once the reformulated product was introduced. This did not include active promotion of the reformulated product, although representatives were told that they could now respond to any customer enquiries by stating that the product was expected to be available in the New Year. Alcon did not consider that this instruction was in breach of the Code since the Code did not apply to 'replies made in response to individual enquiries from members of the health professions or appropriate administrative staff'.

As part of their promotional activities for Systane representatives were also instructed to reinforce that: Systane did not contain BAK but was preserved with Polyquad; BAK was associated with ocular surface toxicity and Polyquad did not exhibit the same ocular surface toxicity as BAK.

Representatives were also encouraged to use the promotion of Systane to raise the subject of dry eye in glaucoma patients and its potential link to the presence of BAK in eye drops used for treatment and to assess the level of interest in this topic, to assist in future targeting of sales activity. To help in this activity, information about BAK and Polyquad was reviewed at the sales meeting and copies of the slides presented were provided. Once again, the representatives were not given copies of these slides.

Promotion of Systane in association with anti-glaucoma products was justified because most glaucoma patients were elderly and the incidence of dry eye disease increased with age and the incidence of dry eye in glaucoma patients was known to be higher than in the population as a whole. It had also been demonstrated that the severity of signs and symptoms of ocular surface disease (including dry eye) in glaucoma patients was directly related to the number of products containing BAK that were used and therefore use of an ocular lubricant preserved

with BAK could make the situation worse.

Systane was not a licensed medicine, although it was listed in the Drug Tariff as a prescribable medical device, and so promotion of this product did not come under the scope of the Code. However, even if it did, the method of promotion described above did not contravene the Code. Clearly, dissemination of information about the potential toxicity of BAK and the comparative performance of Polyquad would be beneficial to Alcon when the Polyquad formulation of Travatan was launched. However, the activities outlined above did not constitute promotion of an unlicensed product. They also did not represent 'teaser advertising' since the activity was not directly linked to promotion of Travatan and substantial information was provided about the preservative contained in Systane in which the intended audience had a legitimate interest and reason to prescribe. Alcon noted that promotion of medicines under the Code did not cover the provision of 'information relating to human health or diseases provided there is no reference, either direct or indirect, to specific medicines' and therefore, in Alcon's opinion, did not cover general discussions about the effects of preservatives in glaucoma patients.

Alcon noted that six items of 'evidence', which claimed to support the allegation, were referenced in the correspondence. Alcon's additional comments on each item were detailed below.

1 **Email from a regional business manager,** 'asking the complainant to 'visit all customers after a speaker meeting to ''discuss the potential of BAK-free.'''

The speaker meeting referred to in this email was an authorized promotional event at which a contracted consultant spoke in support of Azarga, which was also used to treat glaucoma; Travatan was not the subject of the meeting. However, as stated above, the potential problems relating to the use of BAK in glaucoma patients and the availability of a BAK-free formulation of Travatan was common knowledge within the ophthalmic community and during the discussion session at the end of the meeting a member of the audience asked about availability of such a product in the UK. This question was answered in the negative by the speaker, although he did mention that such a product would be available in the near future.

The email was sent to the two representatives who had organised the meeting and encouraged them to build on the speaker's endorsement of Azarga and comments that he made about a competitor product, Lumigan, and also to discuss the potential of 'BAK-free'. This last comment was not to encourage the representatives to promote Travatan outside of the terms of its marketing authorization but to follow the cycle strategy outlined above. All of these instructions were in line with the promotional strategy for this cycle, outlined above.

2 **Hearsay (unsubstantiated),** 'I (the complainant) believed that a [competitor company] had contacted […],Alcon and he had denied all allegations. Five days later, […] and the other two regional managers had telephoned some representatives, not all, to ask them not to discuss BAK-free Travatan.'

Alcon submitted that on 10 November 2010, it received a telephone call from the medical director of a competitor company suggesting that Alcon had promoted a Polyquad preserved formulation of Travatan. This accusation clearly misinterpreted the nature of Alcon's promotional activity and was therefore denied. However, as a result of this call and a follow-up email Alcon's regional business managers were instructed to reinforce the nature of the intended promotional activity to their representatives and to ensure that the Polyquad preserved formulation of Travatan was not directly mentioned in association with this activity. A copy of relevant email correspondence was provided. This correspondence was entirely compatible with the promotional activity already outlined. The competitor company had not taken the matter any further and Alcon submitted that if it had 'actively promoted' the reformulated product, as alleged, the competitor company would surely have been able to gather evidence to pursue a complaint.

3 **Hearsay (unsubstantiated),** 'Myself [the complainant] and a number of representatives have call rates in Alcon's call reporting system which stated that they had discussed this on every available opportunity.'

As stated previously, it was Alcon's intention that its representatives should discuss the potential problems with BAK and the benefits of Polyquad as part of their promotion of Systane and that they could confirm the impending availability of a BAK-free formulation of Travatan if directly questioned. It was not surprising therefore that this should have been mentioned in a representative's call notes. Unfortunately, these call notes were generally used to monitor call patterns and activity and the content was often not scrutinised in detail. Any indication that certain representatives had not adhered to stated company policy with regard to the promotion of Travatan might therefore not necessarily have been noted at the time, unless it was widespread.

As a result of this complaint, Alcon had reviewed its call reporting system records for the complainant's manager's representatives for the period from the last sales meeting to the end of November and found no notes of the type mentioned. However, 40 reports from 3,552 mentioned 'Travatan BAK-free' or 'BAK-free' in association with Travatan rather than Systane. Alcon noted that it had generally been impossible to tell from the report whether any discussion recorded was initiated by the representative or the doctor. Alcon summarised each representative's reports and noted that 22 of the 40 reports (55%) related to one person. Five representatives reported mentioning the reformulated Travatan. Five representatives had not mentioned the reformulated product. Full details of

the reports were provided.

In Alcon's view, the pattern of reporting was not consistent with the allegation of 'active promotion' of the reformulated product but was consistent with the promotional strategy outlined above.

4 **Email from Alcon sent to sales** representatives containing information 'to help them understand what Polyquad was and how they could sell to their customers'.

Alcon submitted that since Systane was actively promoted, it was understandable that it should provide detailed information about Polyquad, the preservative contained therein. As stated above, a presentation on Polyquad was given at the last sales meeting during discussions about Systane.

5 **Email from a sales representative,** 'asking how to answer a formulary pharmacist'.

Alcon stated that this request related to the approved 'in-use life' of Systane, an ocular lubricant preserved with Polyquad, which was 60 days, compared with the 28 day 'in-use life' that applied to most eye drops; it did not relate to Travatan. The complainant's mistake in this regard indicated either their lack of understanding or the mischievous nature of their complaint.

6 **Email from Alcon** 'which asked representatives to no longer promote BAK-free as there had been a complaint from the ABPI.'

Alcon stated that the email in question (a copy was provided) was sent on 24 November to all sales teams after Alcon was notified of the complaint. There was no mention of the ABPI in the email and nor were representatives asked 'to no longer promote BAK-free' as alleged. This would have made no sense, since, as clarified above, they had never been told to promote the reformulated Travatan but had simply been instructed that they could inform customers of its regulatory status, if asked. However, in view of the possibility of further misinterpretation of Alcon's actions, it seemed appropriate to instruct representatives to refrain from even this very limited activity and to 'ensure that there are absolutely no conversations regarding this product until we have a product licence'.

This step was therefore taken purely to ensure that there could be no further misunderstanding of Alcon's promotional objectives and selling focus either internally or externally.

The Authority requested that Alcon send certain information, as part of its response, as listed below.

- Copies of all emails sent by the complainant's manager to his team about Travatan BAK free.

There were no such emails.

- Copies of representatives' call notes from his area, which refered to Travatan BAK-free.

  As stated earlier, Alcon had reviewed 3,552 call records for the period concerned from the ten representatives who reported to him. Forty of those reports either mentioned 'Travatan BAK-free' or the words 'BAK-free' directly linked to promotion of Travatan, 55% of which related to one person. Full details of those reports were provided. In Alcon's view, this number of reports and the nature of the reports concerned, was entirely consistent with the promotional activity outlined above and was not consistent with 'active promotion' of reformulated Travatan before the grant of a marketing authorization, as alleged.

- Copies of all representatives' briefing materials (including emails) which referred to Travatan BAK-free.

There were no such materials, with the exception of the slide set that was provided, a copy of which was not given to the representatives.

Summary and Conclusions

- The allegation had been made by an employee of Alcon who was dismissed due to failure to adhere to company procedures and might be vindictive or mischievous in nature.
- No substantial evidence was provided, or was available, to support the allegation.
- The benefits of Polyquad in patients with ocular surface disease (including glaucoma patients) were discussed. However, this was directly linked to Systane and not to Travatan.
- Representatives were permitted to confirm the impending availability of a reformulated Travatan in the two months before the marketing authorization was obtained, but only in response to a direct enquiry, in line with the requirements of the Code.
- At the first sign that Alcon's promotional activity might be misinterpreted or that some representatives might have deviated from their instructions (a communication from a competitor company), Alcon reinforced, to its representatives, the importance of complying with the Code.

In view of the above and the lack of any substantial evidence provided to support the allegation, Alcon denied any breach of Clauses 2, 3.1, 9.1 or 15.9.

In response to a request for further information, Alcon explained that the original marketing authorization for Travatan 40 micrograms/ml eye drops, solution was granted in November 2001. Since then, a number of variations had been filed to update the dossier, the last of which proposed an excipient change from BAK to Polyquad. This variation was formally approved by the European Commission on 29 November 2010. Therefore, the regulatory status of Travatan from the beginning of October through to 24 November 2010 was that the approved

formulation contained BAK.

As described above, the licence had been approved for over 10 years and it was only the status of the variation to this product licence, proposing the change in an excipient, that was referred to in an email to the representatives. Therefore, Alcon submitted that Travatan (preserved with BAK) and Travatan (preserved with Polyquad – so called 'BAK-free') were one and the same marketing authorization.

Alcon provided copies of the summary of product characteristics (SPC) for Travatan before and after the approval of the variation.

PANEL RULING

The Panel noted that when it received the complaint Travatan preserved with Polyquad was still the subject of a product licence variation. The formulation for which Alcon held a licence at that time was Travatan preserved with BAK. At a meeting held on 30 September/1 October, representatives were briefed on the revised formulation. In the last slide they were instructed that if ophthalmologists asked them about BAK-free Travatan they were to 'Explain that Alcon will introduce (within the new year) NEW Travatan BAK FREE soon, and explain that the new formulation has proven to be as powerful as the existing Travatan but with a better tolerability profile'. The Panel noted that this instruction went beyond Alcon's submission to the Authority that representatives could simply inform customers of the regulatory status of BAK-free Travatan if asked. The Panel noted Alcon's implied submission that replies made in response to individual enquiries from members of the health professions and appropriate administrative staff were not considered to be promotion. The Panel further noted, however, that to take the benefit of not being seen as promotion, such replies had to be in response to an unsolicited enquiry, relate solely to the subject matter of that enquiry, be accurate and not be misleading and not be promotional in nature. In that regard the Panel did not consider that the answer suggested by Alcon which referred to the efficacy and tolerability of a product, in response to a general enquiry about BAK-free Travatan could take the benefit of that exemption. In the Panel's view the suggested answer promoted BAK-free Travatan.

The Panel noted that as a result of this complaint, Alcon emailed its representatives on 24 November and asked them to ensure that there were absolutely no conversations about Travatan BAK-free until it had a product licence. An analysis of the call records from one region showed that one representative in particular regularly referred to BAK-free Travatan from early October until early November. A typical entry by that individual read 'Briefly mentioned Travatan in terms of absolute IOP [intra-ocular pressure] drop, control of diurnal fluctuations, tolerability, price and future BAK free formulation'. It appeared from the call notes that any discussion about BAK-free Travatan had been initiated by the representative and not a health professional. In that regard the Panel noted Alcon's submission that the content of call notes was often not scrutinised in detail and that any indication that a representative had not adhered to company policy might not be picked up at the time unless the practice was widespread. The Panel was concerned about the company's approach which it considered was unacceptable.

The Panel noted that Alcon's product, Systane (a device), was an ocular lubricant preserved with Polyquad and could be promoted. Representatives were instructed to reinforce the message that Systane did not contain BAK, that BAK was associated with ocular surface toxicity and that Polyquad did not exhibit the same ocular surface toxicity as BAK. Representatives were also encouraged to use the promotion of Systane to raise the subject of dry eye in glaucoma patients and its potential link to the presence of BAK in eye drops used for treatment and to assess the level of interest in this topic to assist targeting of future sales activity. In the Panel's view it was likely that the discussion of Systane and problems of dry eye in glaucoma would solicit questions about BAK-free treatments for the condition.

The Panel considered that, on the balance of probabilities, Alcon representatives had promoted BAK-free Travatan before the grant of a marketing authorization which permitted the sale or supply of that formulation. A breach of Clause 3.1 was ruled.

The Panel further considered that the presentation used to brief the representatives in September/October, which encouraged them to discuss and make claims for Travatan BAK-free, advocated a course of action which was likely to lead to a breach of the Code. A breach of Clause 15.9 was ruled.

The Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel, however, did not consider that the activity was such as to bring discredit upon the industry and no breach of Clause 2 was ruled.

Complaint received **24 November 2010**

Case completed **14 March 2011**