CASE AUTH/2150/7/08

GENERAL PRACTITIONER v PFIZER

Toviaz journal advertisements

A general practitioner complained about two advertisements for Toviaz (fesoterodine) issued by Pfizer. One advertisement (published in July 2008) was a revised version of a previous advertisement. At issue were claims comparing the efficacy of Toviaz with tolterodine (Pfizer's product Detrusitol) in the treatment of overactive bladder syndrome (OAB).

The detailed response from Pfizer is given below.

The complainant noted that the phrase 'Article in press' had been used in both advertisements in support of two different, although similar, claims. In the original advertisement this was clearly false as the article in question was not actually in press until 18 July 2008 when it was available online for the first time. The complainant stated that if a journal had agreed to publish a manuscript the usual convention was to state that it had been 'accepted' for publication. The complainant presumed that Pfizer had used 'Article in press' to suggest that this publication, which it had sponsored, had already been accepted by a prestigious peer reviewed journal and so lend gravitas to the claims to which it referred.

The Panel considered that as the article in question, Chapple *et al* (2008), had been accepted for publication in March 2008 it was not unacceptable to describe it as an 'Article in press' in advertisements prepared in May and June 2008; readers would understand that the study was to be published whether such publication was in print or online. The phrase was not misleading or incorrect. No breach of the Code was ruled.

The complainant alleged that the two claims at issue were misleading and not supported by Chapple *et al*. The complainant noted that the claim in the original advertisement 'Toviaz 8mg demonstrated improvements with statistical significance vs tolterodine ER in important treatment outcomes' did not include p values. The claim in the revised advertisement 'By the end of treatment, Toviaz 8mg was significantly better than tolterodine ER 4mg in improving a number of important endpoints; specifically, severe urgency with UUI per 24 hours, mean volume voided per micturition, continent days per week and UUI episodes per 24 hours' was asterisked to a footnote in smaller type 'Analysis of Toviaz 8mg vs tolterodine ER was not part of the original study plan. Starting dose 4mg titrated up to 8mg for more efficacy'.

The complainant stated that 'significantly better than' in the revised advertisement invited readers to assume that not only was the significant superiority of Toviaz 8mg clinically relevant but also statistically significant compared with Toviaz 4mg [sic]. This was misleading.

The footnote highlighted that the claim was based on an unplanned retrospective analysis after unblinding data from two studies and which focussed inappropriately on selective outcome variables in the knowledge that the primary efficacy variable showed no difference between Toviaz 4mg and 8mg. Indeed, it appeared that the statistical analysis section described only planned comparisons of Toviaz vs placebo in the individual studies. There was no mention of any intention to pool study data or undertake a planned meta-analysis that would validate the introduction of a specific comparison of Toviaz 8mg vs 4mg. The complainant alleged that this was a blatant example of data massaging.

Whilst the footnote provided additional information, it fundamentally altered the interpretation and message of the claim as it appeared in the original advertisement and revised advertisement but was also not capable of being substantiated. The complainant understood that the Code did not permit misleading headlines to be corrected by a footnote.

The complainant considered that the Authority should address this potentially serious matter with Pfizer and ask why Pfizer should not be subject to an enquiry as to why such shoddy and misleading promotional materials were used. Given Pfizer's propensity to mislead, make false statements and fail to comply with previous undertakings (ie Case AUTH/2130/0/08) the complainant believed Pfizer had brought the ABPI into disrepute and must face appropriate sanctions.

The Panel noted that there was some confusion on the complainant's part as to the claims being made and to the basis of those claims. The Panel considered the claims as written and referenced in the advertisements at issue.

The Panel noted that the study to which the claims were referenced (Chapple *et al* 2008) was a post hoc analysis of a phase 3 study by Chapple *et al* (2007). The original study had investigated the efficacy, tolerability and safety of Toviaz 4mg and 8mg vs placebo in OAB. The study included a tolterodine ER 4mg arm as an active control. Both doses of Toviaz were significantly better than placebo in improving the symptoms of OAB. Efficacy was more pronounced with Toviaz 8mg than with other treatments. The post hoc study

extracted from the original study only the data relating to Toviaz 8mg, tolterodine ER 4mg and placebo and examined the results for the primary endpoint (voids/24h), the two co-primary endpoints (urgency urinary incontinence (UUI) episodes/24h and treatment response), several secondary endpoints and health related quality of life HRQoL. The data showed that by week 12 patients in both active-treatment groups showed significant improvements in most bladder diary variables and treatment response rates compared with placebo. Toviaz 8mg was statistically significantly better than tolterodine ER 4mg for improving UUI episodes, severe urgency plus UUI, mean voided volume and number of continent days/week. In addition the Toviaz and tolterodine groups showed significantly greater improvements in HRQoL than the placebo group. A major improvement in the severity of bladder-related problems was reported by 39% of the Toviaz group and 34% of the tolterodine ER groups v 25% of those on placebo ($p \leq 0.01$). The author stated that one of the limitations of the study was that it was a post hoc analysis of a study which was not powered for a comparison between active treatments or for HRQoL. Prospective studies were under way. The lack of consensus on measurement of the urgency classification was described as another shortcoming.

The Panel noted that the claim in the first advertisement 'Toviaz 8mg demonstrated improvements with statistical significance vs tolterodine ER in important treatment outcomes' was very general. The Panel was concerned that the post hoc comparison of Toviaz 8mg with tolterodine ER 4mg was not part of the original study plan and that the original study was not powered for such a comparison. The Panel thus considered that the claim was misleading, and ruled a breach of the Code which was accepted by Pfizer. Chapple *et al* (2008) did not substantiate the claim and thus a further breach of the Code was also ruled, which was upheld on appeal by Pfizer.

With regard to the second advertisement the Panel noted that it was a well established principle under the Code that a claim could not be qualified by a footnote. It considered that given the statements in Chapple *et al* (2008) about the limitations of the study, the fact that it was a post hoc analysis and that Chapple *et al* (2007) was not powered for a between treatments comparison meant that the claim 'Toviaz 8mg was significantly better than tolterodine ER 4mg in improving a number of important endpoints; specifically…' was misleading and not capable of substantiation. Breaches of the Code were ruled, which were upheld on appeal by Pfizer.

The position was further confused by the second part of the footnote 'Starting dose 4mg titrated up to 8mg for more efficacy'. This did not apply to Chapple *et al* (2007) where patients received medicine at the same dose throughout the study. It appeared to be more general information about the use of Toviaz as according to its summary of product characteristics the recommended starting dose of 4mg once daily could, according to individual response, be increased to 8mg once daily (the maximum daily dose).

Overall, the Panel considered that high standards had not been maintained and a breach of the Code was ruled, which was upheld on appeal by Pfizer.

The Panel noted that Clause 2 of the Code was reserved as a sign of particular censure. It considered on balance that the circumstances did not warrant a ruling of a breach of that clause. This ruling was upheld on appeal by the complainant.

A general practitioner complained about the promotion of Toviaz (fesoterodine fumarate) by Pfizer Limited. Pfizer also marketed Detrusitol (tolterodine). Both products were for the symptomatic treatment of overactive bladder syndrome (OAB).

This case was considered under the 2008 Constitution and Procedure. When writing to Pfizer the Authority asked it to comment in relation to Clauses 2, 7.2, 7.4 and 9.1 of the Code which were the same in the 2008 Code as in the 2006 Code.

1 Use of the phrase 'Article in press'

The phrase 'Article in press' appeared as a reference in an advertisement (TOV097b) and in the revised edition of that advertisement (ref TOV162) which was published in Geriatric Medicine (July 2008).

The 'Article in press' (Chapple *et al* 2008) was used as a reference for the claim 'Toviaz 8mg demonstrated improvements with statistical significance vs tolterodine ER in important treatment outcomes' in the original advertisement (TOV097b). It was also used as a reference to the claim 'By the end of treatment, Toviaz 8mg was significantly better than tolterodine ER 4mg in improving a number of important endpoints; specifically, severe urgency with [urgency urinary incontinence] UUI per 24 hours, mean volume voided per micturition, continent days per week and UUI episodes per 24 hours' in the updated advertisement (TOV162).

COMPLAINT

The complainant stated the claim 'Toviaz 8mg demonstrated improvements with statistical significance vs tolterodine ER in important treatment outcomes' did not include p values. It was referenced to Chapple *et al* ('Clinical efficacy, safety, tolerability of once-daily fesoterodine in subjects with an overactive bladder') which was cited as being an 'Article in press' in the British Journal of Urology International. This was clearly false given that it was not actually in press until 18 July 2008 when it was available online for the first time! The

complainant stated that if the journal in question had agreed to publish the manuscript the usual convention was to state that the publication was 'accepted' for publication.

The complainant presumed the reason why Pfizer considered the use of the wording 'Article in press' appropriate, thereby suggesting that this Pfizer sponsored publication had already been accepted by a prestigious peer reviewed journal, was because it lent gravitas to the promotional claims to which it referred.

In the revised advertisement (TOV162) the same misleading wording with regard to the publication status of Chapple *et al* was used in support of a similar claim.

RESPONSE

Pfizer explained that the phase 3 clinical trial program for Toviaz consisted of two key trials. These were both published as primary publications: Chapple *et al* (2007) and Nitti *et al* (2007). As was common with clinical trial programmes, subsequent publications and analysis had been produced. One of these publications was a further analysis of data regarding maximum recommended doses of fesoterodine (8mg) and tolterodine (4mg). This was currently published online as Chapple *et al* (2008) ('Comparison of fesoterodine and tolterodine in subjects with overactive bladder. British Journal of Urology International. (Epub ahead of print)').

The complaint was wrong to state that the claim 'Toviaz 8mg demonstrated improvements with statistical significance vs tolterodine ER in important treatment outcomes' was referenced to Chapple *et al* (2007) ('Clinical efficacy, safety and tolerability of once-daily fesoterodine in subjects with overactive bladder'). This particular manuscript was accepted for publication by the journal European Urology on 6 July 2007; published online on 17 July 2007 and appeared in Issue 4 of Volume 52 on October 2007 and was referenced as such when used.

The above claim, as used in both advertisements (TOV097b and TOV162) was substantiated from the correctly referenced publication Chapple *et al* (Article in press).

When the advertisements were prepared (May 2008 – TOV097b and June 2008 – TOV162) the term 'Article in press' was accurate as the article had been accepted by the British Journal of Urology International on 28 March 2008 and published online on 21 July 2008. The statement 'Article in press' was an acceptable and common phrase to describe a manuscript that had been submitted and accepted by a journal, but where an imminent date of publication had not been provided by the journal. It was not misleading nor false as the complainant had suggested.

Pfizer therefore, refuted a breach of Clauses 2, 7.4 and 9.1.

PANEL RULING

The Panel noted that when referring to the Chapple *et al* article that was yet to be published, the complainant had cited the title of Chapple *et al* (2007). The Panel considered that as Chapple *et al* (2008) had been accepted for publication it was not unacceptable to describe it as an 'Article in press'; readers would understand that the study was to be published whether such publication was in print or online. The phrase was not misleading or incorrect. No breach of Clause 7.2 was ruled.

2 Claims 'Toviaz 8mg demonstrated improvements with statistical significance vs tolterodine ER in important treatment outcomes' (TOV097b) and **'By the end of treatment, Toviaz 8mg was significantly better than tolterodine ER 4mg in improving a number of important endpoints; specifically, severe urgency with UUI per 24 hours, mean volume voided per micturition, continent days per week and UUI episodes per 24 hours'** (TOV162).

Both claims were referenced to Chapple *et al* (2008) (Article in press). The second claim was asterisked to a footnote in smaller type 'Analysis of Toviaz 8mg vs tolterodine ER was not part of the original study plan. Starting dose 4mg titrated up to 8mg for more efficacy'.

COMPLAINT

The complainant alleged that the claims were misleading and not supported by Chapple *et al* (2008). The first claim (in TOV097b) did not include the p values and the footnote to the second claim (in TOV162) was barely legible. The wording 'significantly better than' invited readers to assume that not only was the significant superiority of Toviaz 8mg clinically relevant but also statistically significant compared with Toviaz 4mg [sic]. This was misleading.

The footnote highlighted that the claim was based upon an unplanned retrospective analysis after unblinding data from two studies and which focussed inappropriately on selective outcome variables in the knowledge that the primary efficacy variable showed no difference between Toviaz 4mg and 8mg. Indeed, it appeared that the statistical analysis section described only planned comparisons of Toviaz vs placebo in the individual studies. The publication made no mention of any intention to pool study data or undertake a planned meta-analysis that would validate the introduction of a specific comparison of Toviaz 8mg vs 4mg.

Given the latter, the complainant had discussed the statistical validity of this claim with a pharmacist colleague. They reviewed the two published

primary studies, upon which Chapple *et al* (2008) was based and it was clear that in these studies the statistical analysis plan started off with micturition frequency in what was described as a sequentially rejective closed-test procedure and then moved on to the next specified endpoints only if this was statistically significant. It was therefore logical to assume that micturition frequency was also the primary variable (or one of the primary variables) for Chapple *et al* (2007). In the latter, however, Chapple *et al* failed to show statistical significance of Toviaz 8mg vs 4mg. Therefore it seemed that there was no statistical basis that justified the statistical testing of other endpoints referred to in the publication and in the revised advertisement; this important clarification was completely missing both in Chapple *et al* (2008) and in the advertisement footnote. Indeed, if Chapple *et al* applied the same method as for the individual study protocols, they had to stop testing after the test for micturition frequency had failed and would have had to declare all endpoints were not statistically significant with respect to differences between Toviaz 8mg vs 4mg.

It therefore appeared that these studies had been selected for discussion in this publication on the basis of their results and called into question the validity of this citation as substantiation of the superiority claim for 8mg Toviaz, in both Toviaz advertisements. Indeed, the timing of this retrospective analysis, which clearly occurred after the unblinding of the data, totally nullified the basis for undertaking any comparison. The complainant alleged that this was a blatant example of 'data massaging'.

Whilst the footnote provided additional information, it fundamentally altered the interpretation and message of the promotional claim as it appeared in the original advertisement and revised advertisement but was also not capable of being substantiated. The complainant understood that the Code did not permit misleading headlines to be corrected by a footnote.

The complainant believed that this unsubstantiated claim was cited in many other Toviaz promotional materials including the Toviaz detail aid (which the Pfizer sales representative did not allow the complainant to have a copy of… was this consistent with the Code?) and promotional flyers (TOV096 and TOV095). The complainant believed these documents must be scrutinised to ascertain the above.

The complainant considered that the Authority should address this potentially serious matter with Pfizer and also ask why Pfizer should not be subject to an enquiry as to why such shoddy and misleading materials were used. Given Pfizer's propensity to mislead, make false statements and fail to comply with previous undertakings (ie Case AUTH/2130/0/08) the complainant believed Pfizer had brought the ABPI into disrepute and must face appropriate sanctions.

RESPONSE

Pfizer stated that the initial advertisement (TOV097b), was withdrawn due to lack of prescribing information (Case AUTH/2130/6/08) and the claim, Toviaz 8mg demonstrated improvements with statistical significance vs tolterodine ER in important treatment outcomes' was no longer used. Pfizer therefore refuted a breach of Clause 7.2.

Pfizer stated that although the publication supporting the claim was clearly separate from the primary publication and was specifically about the comparison of fesoterodine and tolterodine (Chapple *et al* 2008), Pfizer included the footnote 'Analysis of Toviaz 8mg vs. tolterodine ER was not part of the original study plan' in the updated advertisement specifically so that readers might obtain a comprehensive and balanced view of the data to form an opinion on the therapeutic value of the medicine. The footnote did not fundamentally alter the interpretation and message of the claim as alleged by the complainant. The footnote was in a clearly legible font size and placed immediately below the claim.

Pfizer therefore, refuted breaches of Clauses 2, 7.2 and 9.1.

In the revised advertisement (TOV162), additional information was included specifically to ensure it was not misleading and clearly reflected the available evidence. The updated advertisement stated 'By the end of treatment, Toviaz 8mg was significantly better than tolterodine ER 4mg in improving a number of important endpoints; specifically, severe urgency with UUI per 24 hours, mean volume voided per micturition, continent days per week and UUI episodes per 24 hours' which made it clear to the reader which outcomes reached a statistical and clinical relevant result and it was appropriately substantiated by its reference.

The complainant had made some fundamental errors in his statistical assessment of the claim. The claim was not based on a pooled analysis of the two primary studies, nor was there any comparison of Toviaz 4mg vs Toviaz 8mg in the paper or in the claim.

Chapple *et al* (2008) used to substantiate the claim was a post hoc analysis of one phase 3 trial, in which fesoterodine 8mg was compared to tolterodine 4mg (Chapple *et al* 2007). Although statistical methods used in post hoc analyses might be similar to the primary methods used in the study they did not necessarily follow the same approach regarding controlling for error rates.

The closed-testing methodology used in the analysis of the three co-primary endpoints in the original fesoterodine phase 3 trials was appropriate for controlling experiment-wise error rates. The need to use such methodology was, however, unusual for over active bladder (OAB) trials in general, since the overwhelming majority of

published OAB studies had one primary endpoint and multiple secondary endpoints.

When performing post hoc analyses Pfizer typically reported p values without adjustments, in order to help understand treatment differences separately, and not in the context of the overall error rate that also considered other comparisons. Generating individual comparison p values was an accepted and common practice when performing post hoc and secondary analyses.

The statistical methods employed in the Chapple *et al* (2008) post hoc analysis were clearly described in the British Journal of Urology International manuscript, which was accepted for publication following peer review and considered level 1b evidence by the journal. This publication was robust, peer-reviewed and accurately portrayed in promotional materials.

Pfizer had never claimed superiority of Toviaz 8mg in any of its materials and strongly objected to any allegation of data massaging. Pfizer did not consider any of its materials to be in breach of Clauses 7.2 or 7.4.

Pfizer submitted that its representatives were not obliged to distribute promotional materials that were not intended for that purpose. Detail aids, which remained the property of Pfizer, were designed to be retained by the representative and used with the health professional as part of a discussion. Promotional items intended to be left with a health professional were designed with that function in mind. This practice was entirely consistent with the Code.

Pfizer did not consider the promotional items mentioned by the complainant had breached the Code and firmly believed that they were properly referenced, accurate and factually correct without being misleading. Pfizer also had maintained high standards and ensured that its items and activities did not diminish the reputation of the industry. Pfizer firmly believed that upon examination of the complainant's concerns, there were no breaches of the Code.

Pfizer aimed to continually review all its promotional materials to ensure they complied with the Code in word and in spirit. It was keen to ensure the highest standard of professional practice and to safeguard the reputation of the industry.

PANEL RULING

The Panel noted that the study to which the claims were referenced (Chapple *et al* 2008) was a post hoc analysis of a phase 3 study by Chapple *et al* (2007). The original study had investigated the efficacy, tolerability and safety of Toviaz 4mg and 8mg vs placebo in OAB. The study included a tolterodine ER 4mg arm as an active control. Both doses of Toviaz were significantly better than placebo in improving the symptoms of OAB. Efficacy was more pronounced with Toviaz 8mg than with other treatments. The post hoc study extracted from the original study only the data relating to Toviaz 8mg, tolterodine ER 4mg and placebo and examined the results for the primary endpoint (voids/24h), the two co-primary endpoints (urgency urinary incontinence (UUI) episodes/24h and treatment response), several secondary endpoints and health related quality of life HRQoL. The data showed that by week 12 patients in both active-treatment groups showed significant improvements in most bladder diary variables and treatment response rates compared with placebo. Toviaz 8mg was statistically significantly better than tolterodine ER 4mg for improving UUI episodes, severe urgency plus UUI, mean voided volume and number of continent days/week. In addition the Toviaz and tolterodine groups showed significantly greater improvements in HRQoL than the placebo group. A major improvement in the severity of bladder-related problems was reported by 39% of the Toviaz group and 34% of the tolterodine ER groups v 25% of those on placebo ($p \leq 0.01$). The author stated that one of the limitations of the study was that it was a post hoc analysis of a study which was not powered for a comparison between active treatments or for HRQoL. Prospective studies were under way. The lack of consensus on measurement of the urgency classification was described as another shortcoming.

The Panel noted that there appeared to be some confusion. Both advertisements included two claims based on Chapple data. Firstly, that Toviaz was effective in relieving the most bothersome symptoms of OAB at both 4mg and 8mg doses referenced to Chapple *et al* (2007) and secondly, the claims comparing Toviaz 8mg with tolterodine ER 4mg (not Toviaz 4mg as submitted by the complainant) referenced to Chapple *et al* (2008). Chapple *et al* (2008) was based on Chapple *et al* (2007) not two studies as stated by the complainant.

The Panel noted that the original study (Chapple *et al* 2007) had demonstrated more pronounced treatment effects with Toviaz 8mg than with tolterodine ER 4mg or Toviaz 4mg. There was no comparison between treatments. Thus it appeared that the complainant's comments about the statistical analysis, in this regard were misguided.

The Panel considered that some of the complainant's comments about Chapple *et al* (2008) were relevant to the comparison of Toviaz 8mg with tolterodine 4mg.

The Panel noted that the claim in the first advertisement (TOV097b) 'Toviaz 8mg demonstrated improvements with statistical significance vs tolterodine ER in important treatment outcomes' was very general. The Panel was concerned that the post hoc comparison of Toviaz 8mg with tolterodine ER 4mg was not part of the original study plan and that the original study was not powered for such a comparison. The Panel

thus considered that the claim was misleading, and ruled a breach of Clause 7.2 which was accepted by Pfizer. Chapple *et al* (2008) did not substantiate the claim and thus a breach of Clause 7.4 was also ruled.

With regard to the second advertisement (TOV162) the Panel noted that it was a well established principle under the Code that a claim could not be qualified by a footnote. It considered that given the statements in Chapple *et al* (2008) about the limitations of the study, the fact that it was a post hoc analysis and that Chapple *et al* (2007) was not powered for a between treatments comparison meant that the claim 'Toviaz 8mg was significantly better than tolterodine ER 4mg in improving a number of important endpoints; specifically…' was misleading and not capable of substantiation. Breaches of Clauses 7.2 and 7.4 of the Code were ruled.

The position was further confused by the second part of the footnote 'Starting dose 4mg titrated up to 8mg for more efficacy'. This did not apply to Chapple *et al* (2007) where patients received medicine at the same dose throughout the study. It appeared to be more general information about the use of Toviaz as according to its summary of product characteristics the recommended starting dose of 4mg once daily could, according to individual response, be increased to 8mg once daily (the maximum daily dose).

Overall, the Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel noted that Clause 2 was reserved as a sign of particular censure. It considered on balance that the circumstances did not warrant a ruling of a breach of that clause.

APPEAL BY PFIZER

Pfizer accepted a breach of Clause 7.2 in relation to the claim 'Toviaz 8mg demonstrated improvements with statistical significance vs tolterodine ER in important treatment outcomes' in TOV097b, as it agreed that the claim could be viewed as too general. Before the complaint was received, Pfizer had withdrawn TOV097b to provide additional information so that there was no doubt about which treatment endpoints had reached statistical significance. The claim 'By the end of treatment, Toviaz 8mg was significantly better than tolterodine ER 4mg in improving a number of important endpoints; specifically severe urgency with UUI per 24 hours, mean volume voided per micturition, continent days per week and UUI episodes per 24 hours' in the subsequent advertisement, TOV162, stated that the significant improvements with Toviaz 8mg compared with tolterodine ER 4mg were relevant to a number of defined endpoints. These endpoints were then clearly specified, with no indication that this statistical significance related to all endpoints measured. Furthermore, a footnote was added to provide further information on the analysis and to ensure that the material was sufficiently complete to enable the reader to form their own opinion; the footnote did not qualify the claim.

Pfizer therefore submitted that the claim in the advertisement TOV162 was not misleading, and not in breach of Clause 7.2.

Pfizer noted that the Panel had ruled a breach of Clause 7.4 in relation to both advertisements TOV097b and TOV162. The Panel was concerned that the post hoc comparison of Toviaz 8mg with tolterodine ER 4mg was not part of the original study plan and that the original study was not powered for between-treatment comparisons (Chapple *et al*).

Pfizer submitted that a post hoc analysis was conducted to explore patterns that were not specified at the time of protocol development. Typically, studies were powered for the primary endpoint(s) only, which in this case was the comparison of the two doses of Toviaz with placebo on the three co-primary endpoints. Generally, neither secondary endpoints nor additional analyses might be statistically powered, and should be regarded as exploratory. Such data might still be able to substantiate claims, provided the materials clearly contained this context information on the nature of the data, so as to ensure the reader was not misled.

Whilst the comparison of the two Toviaz doses with tolterodine ER was not the primary endpoint in the phase 3 trial, it was of clinical interest and had been pre-specified in the statistical analysis plan (provided). The comparison was carried out on the full analysis set with the last observation carried forward (LOCF), and the patient populations were not selected, altered or modified compared with those used for the pre-specified analyses (Chapple *et al*). The results for the co-primary endpoint urge incontinence showed that the 95% confidence interval for the treatment difference of 0.48 episodes/day between Toviaz 8mg and tolterodine ER 4mg was (-0.92; -0.05) (Pfizer data on file). Since this did not contain zero this indicated a difference between the two treatments with respect to urge incontinence.

The statistical methods used for the comparison of Toviaz 8mg with tolterodine ER were clearly described in the manuscript which was accepted for publication following peer review and considered level 1b evidence by British Journal of Urology International, a well respected, peer-reviewed journal. Pfizer therefore did not agree that the claims in the advertisements TOV097b and TOV162 were unsubstantiated by the post hoc evidence, and did not agree that these materials were in breach of Clause 7.4.

Pfizer stated that it was committed to producing promotional materials of a high standard that

conformed to the letter and the spirit of the Code. Pfizer's continuous review of promotional materials ensured an accurate reflection of up-to-date clinical data in a manner that encouraged transparency and gave the reader a comprehensive view of all the available evidence. Through rigorous internal processes Pfizer strove to ensure that it truthfully portrayed its clinical evidence to health professionals.

Pfizer submitted that it had maintained high standards relating to its promotion of Toviaz, and therefore denied a breach of Clause 9.1.

COMMENTS FROM THE COMPLAINANT

The complainant alleged that the main claim comparing the comparative efficacy of Toviaz 8mg vs tolterodine ER could not be substantiated or supported by the cited reference or the footnotes adopted for the very clear and salient reasons described by the Panel in its ruling; the complainant entirely agreed with these rulings.

Indeed, Pfizer's response clearly demonstrated that the original study never intended to produce robust and statically valid comparative data, which was normally what one expected to support a promotional claim of superior efficacy of one medicine versus another as this particular claim did. Indeed, the statistical analysis plan that Pfizer referred to explicitly stated that the comparison was primarily planned to be between Toviaz treatment groups and placebo. The only valid comparison involving tolterodine ER was with respect to placebo and even this was only undertaken to check assay sensitivity in an exploratory manner; hardly a clear and definitive basis upon which to make commercial claims of superior efficacy of Toviaz 8mg over tolterodine ER! Indeed where the statistical analysis plan mentioned a comparison of Toviaz with tolterodine ER it specified that it was with respect to the two doses of Toviaz and that it was exploratory and no p-values would be produced (ie this comparison was not statistically valid for the purposes of making promotional claims that one would reasonably expect to be based upon data that were both statistically and clinically significant).

Notwithstanding the Panel's ruling that an exploratory analysis could not be the basis on which to invite bold commercial claims of superiority for obvious reasons one must also then ask why the comparison between Toviaz 4mg and tolterodine ER was also not used in the promotional claim; surely this would be consistent with the statistical analysis plan. The complainant alleged that this was a clear example of cherry-picking the data and arguments that suited Pfizer. The complainant would not be surprised if the efficacy of Toviaz 4mg was equivalent or worse than that of tolterodine ER; a fact that would obviously not suit Pfizer's promotional strategy of promoting a switch of tolterodine ER 4mg patients to Toviaz 8mg which was clearly likely to be more efficacious than Toviaz 4mg. In fact, in the event that the statistical analysis plan allowed a valid/robust comparison capable of supporting promotional claims without qualifications (which it did not in this case), one might even question whether the comparison of the highest dosage of Toviaz (also an extended release formulation) against tolterodine ER 4mg was fair given that mg-for-mg it did not compare equivalent dosages of the two virtually similar medicines.

The complainant was sure that all ABPI companies would like to develop promotional campaigns based on exploratory data supported by post hoc analysis conducted to explore patterns that were not specified at the time of protocol development; it was called data massaging and was certainly a lot less expensive and time consuming than undertaking robust clinical studies. Indeed if Pfizer's statement did not clearly demonstrate why breaches of the Code, including Clause 2, were not warranted, then the complainant was not sure what did.

Pfizer was obviously unabashed about its reliance on what was essentially dodgy/spurious data in support of a cynical campaign which essentially now advised all prescribers of tolterodine ER, that for the many years that Pfizer promoted tolterodine ER as the best in class and encouraged its prescription for the management of OAB it had in fact got it wrong especially now that its patent expiry was imminent. The misleading reasons Pfizer promoted as to why doctors should now prescribe Toviaz instead of tolterodine ER was that the efficacy/mode of action/route of metabolism, side-effect profile of tolterodine ER were all somehow inferior to the recently launched Toviaz where patent expiry and the bottom-line were not such an urgent concern.

Prescribers expect to be provided with data/information and promotional messages in a manner and of a quality consistent with the standards prescribed by the Code. The Toviaz promotional materials that the complainant had seen both in the UK and at various international congresses, since its launch fell well below this.

APPEAL BOARD RULING

The Appeal Board noted that Pfizer had appealed the Panel's ruling of a breach of Clause 7.4 in relation to the claim 'Toviaz 8mg demonstrated improvements with statistical significance vs tolterodine ER in important treatment outcomes'. Pfizer submitted that the claim was capable of substantiation by Chapple *et al* (2008) notwithstanding the fact that it had accepted that the claim was misleading in breach of Clause 7.2. The Appeal Board was concerned that the post hoc comparison of Toviaz 8mg with tolterodine ER 4mg was not part of the original study plan and that the original study was not powered for such a comparison. Chapple *et al* (2008) did not substantiate the claim and thus the Appeal Board

upheld the Panel's ruling of a breach of Clause 7.4 of the Code. The appeal on this point was unsuccessful.

With regard to the second advertisement (TOV162) the Appeal Board considered that the claim at issue, '… Toviaz 8mg was significantly better than tolterodine ER 4mg in improving a number of important endpoints; …' also referenced to Chapple *et al* 2008 implied statistical significance which was not so. The Appeal Board did not accept Pfizer's submission at the appeal that it was not claiming statistically significant superiority. There was a clear claim of superiority in the advertisement and this would be read as being clinically and statistically significant. The statistical analysis plan for Chapple (2008) had stated that the comparison of the two doses of Toviaz with tolterodine ER would only be done as an exploratory analysis and no p-values would be provided. Although a footnote stated 'Analysis of Toviaz 8mg v tolterodine ER was not part of the original study plan' otherwise misleading claims could not be so qualified. The Appeal Board considered that given the data upon which it was based, the claim was misleading and had not been substantiated. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.4. The appeal on this point was unsuccessful.

The position was further confused by a second footnote which stated 'Starting dose 4mg titrated up to 8mg for more efficacy'. This did not apply to Chapple *et al* where patients received Toviaz at the same dose (4mg or 8mg) throughout. It appeared that the footnote gave more general information about the use of Toviaz; according to its summary of product characteristics (SPC) the recommended starting dose was 4mg once daily which could, according to individual response, be increased to 8mg once daily (the maximum daily dose).

Overall, the Appeal Board considered that high standards had not been maintained and it upheld the Panel's ruling of a breach of Clause 9.1 of the Code. The appeal on this point was unsuccessful.

During its consideration the Appeal Board noted that the Toviaz SPC stated that 'The recommended starting dose is 4mg once daily. Based upon individual response, the dose may be increased to 8mg once daily. The maximum daily dose is 8mg'. The Appeal Board noted that in Chapple *et al* (2007) patients were started on either a 4mg or 8mg dose of Toviaz. The patients started on the maximum daily dose of 8mg Toviaz had not been treated in accordance with the Toviaz SPC.

APPEAL BY THE COMPLAINANT

The complainant was disappointed regarding the Panel's decision not to rule a breach of Clause 2. This seemed particularly at odds with the decision that Pfizer had not maintained high standards. Arguably the need to maintain high standards not only compromised prescriber's confidence but also patient safety and as such any ABPI company that was censured with respect to Clause 9.1 had also brought the industry into disrepute.

An analogy in this regard was the consequences faced by health professionals who failed to maintain high standards in communicating erroneous, misleading advice/information to patients; in this event the General Medical Council Fitness to Practice Committee was very likely to impose some very stringent sanctions … not simply a monetary fine, which was probably considered to be loose change to companies such as Pfizer. A ruling of a breach of Clause 2 was appropriately punitive and should be considered by the Appeal Board.

Finally, the complainant also wanted reassurance that Pfizer would be required to address and implement the Panel's rulings across all of the Toviaz promotional materials given that the latter all contained claims which were ruled to be in breach of the Code.

COMMENTS FROM PFIZER

Pfizer submitted that a breach of Clause 9.1 did not automatically warrant a breach of Clause 2 which was a sign of particular censure and was reserved for circumstances in which a company brought discredit to, and reduced confidence in, the pharmaceutical industry. Pfizer did not believe the particulars of this case fell into that category.

Pfizer did not agree with the complainant that the promotional claims in question were detrimental to patient safety or prescriber confidence. Pfizer was committed to producing high quality promotional materials that complied to both the letter and spirit of the Code.

FINAL COMMENTS FROM THE COMPLAINANT

The complainant confirmed that the latter aspects of his response to Pfizer's appeal also referred to why he still considered a breach of Clause 2 was warranted regardless of Pfizer's comments on his appeal regarding this particular clause.

APPEAL BOARD RULING

The Appeal Board noted that Clause 2 of the Code was reserved as a sign of particular censure. Although noting its rulings above, the Appeal Board did not consider that the circumstances warranted a ruling of a breach of that clause. The Appeal Board upheld the Panel's ruling of no breach of Clause 2.

Complaint Received **25 July 2008**

Case Completed **28 October 2008**