ANONYMOUS CONSULTANT PHYSICIAN v SANOFI-AVENTIS and PROCTER & GAMBLE

Actonel leavepiece

An anonymous consultant physician complained about a leavepiece for Actonel (risedronate sodium) issued by Sanofi-Aventis and Procter & Gamble, as the Alliance for Better Bone Health (ABBH).

The complainant took issue with the selective conclusions in the leavepiece at issue which referred to Silverman *et al* (2007) (the risedronate and alendronate (REAL) cohort study). The leavepiece contended that the REAL study unequivocally demonstrated a reduced incidence of hip fracture for Actonel relative to alendronate.

The complainant considered that single-patient, meta-analysis of results informed by randomized, controlled trials was the best type of evidence but in the absence of such data, evidence obtained from observational studies was probably reasonable. That was clearly not the case in this situation.

A substantial body of evidence concerning the efficacy of medicines such as Actonel and alendronate suggested fracture rates, including hip fracture, might be halved during three years of therapy. No randomized, controlled trial had demonstrated differential anti-fracture efficacy for the two products in question. Indeed, comparative studies had shown superior response in terms of surrogate markers (bone density) for alendronate rather than Actonel.

Perhaps most importantly, current guidelines from the National Institute of Health and Clinical Excellence (NICE) did not recognise a difference in terms of the relative efficacy of these products. The current draft of the updated guidelines recommended alendronate as first line treatment for postmenopausal osteoporosis and explicitly did not recommend Actonel as appropriate use of NHS resources. Whilst this was draft guidance, and therefore not to be relied upon per se, the rationale for it related to the substantial difference in price between the two; alendronate had been available generically in the UK for almost two years and had a Drug Tariff price of £7.22 compared with £20.30 for weekly Actonel.

The results of the pharmacoeconomic analysis conducted by NICE for two probably similarly efficacious products, predictably, and correctly in the complainant's view, dominated for alendronate over Actonel in all modelling scenarios.

The REAL study was not representative of the substantial evidence base for Actonel and alendronate. Furthermore, the complainant considered that the inappropriately aggressive (and inaccurate) conclusions presented within the leavepiece attempted to dissuade practitioners from using alendronate in preference to Actonel, contrary to current and likely future NICE guidance.

The Panel noted that there were differences in the indications for Actonel and Fosamax. In the UK Actonel Once Weekly was indicated for the treatment of established postmenopausal osteoporosis to reduce the risk of hip fractures as well as for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral fracture. Whereas Fosamax Once Weekly was indicated for the 'Treatment of postmenopausal osteoporosis, 'Fosamax' reduces the risk of vertebral and hip fractures'.

The Panel noted that the leavepiece at issue was headed 'In established postmenopausal osteoporosis' and referred to the REAL study which had been sponsored by the ABBH. The study had been conducted in the US and was a retrospective observation of bisphosphonate patients which compared the annual incidence of fracture with either once-weekly 35mg Actonel (n=12,215) or once-weekly alendronate (n=21,615). Women for inclusion were aged 65 and over with any use of once-a-week dosing of Actonel or alendronate after July 2002 (when once-weekly versions of both therapies became available). The Panel noted that 8% of the alendronate patients received only 35mg weekly compared with 70mg weekly which was the dose licensed in the UK for the treatment of postmenopausal osteoporosis. Page 2 of the leavepiece presented a comparison of the incidence of hip fracture during therapy at 6 and 12 months. The percentage of women with a hip fracture on alendronate was 0.29% and 0.58% at 6 and 12 months respectively. The percentage of women with a hip fracture on Actonel was 0.17% and 0.37% at 6 and 12 months respectively; an absolute difference of 0.12% (p=0.02) and 0.21% (p=0.01) respectively. In that regard the Panel queried the clinical significance of the results. The relative reductions for patients on Actonel were 46% and 43% at 6 and 12 months respectively. The leavepiece presented that data in a bar chart which noted the absolute percentages of women with a hip fracture together with prominent downward arrows showing the relative differences of 46% and 43% at 3 and 6 months respectively. Below the bar chart was the claim 'Actonel reduces the incidence of hip fracture compared to alendronate as early as 6 months in real life'.

The REAL study concluded that, 'within this observational study of clinical practice, a cohort of patients receiving risedronate had lower rates of hip

and nonvertebral fractures during their first year of therapy than a cohort of patients receiving alendronate. These results do not appear to be explained by baseline differences in fracture risk between cohorts. In addition, the observed rates of fracture were consistent with the fracture rates in clinical trials. Thus it appears, patients receiving risedronate are better protected from hip and nonvertebral fractures during their first year of therapy than patients receiving alendronate'.

The Panel considered that the leavepiece was more positive about the differences between Actonel and alendronate than the study authors. In that regard, although NHS resources were not referred to per se, the leavepiece encouraged the use of Actonel and not alendronate. Although a statistically significant difference between the two products had been identified in favour of Actonel, the absolute difference was small. Furthermore the results might have been biased against alendronate given that 8% of the alendronate patients had only received half the weekly dose licensed for the treatment of established postmenopausal osteoporosis ie 35mg vs 70mg.

Taking all the factors into consideration the Panel considered that the leavepiece was misleading and thus ruled breaches of the Code.

Upon appeal by Sanofi-Aventis and Procter & Gamble the Appeal Board noted that the REAL study authors had performed a sensitivity analysis whereby the 1768 patients who received 35mg alendronate were removed from the study population and the data was reanalysed. The ABBH submitted that the result was consistent with the primary analysis and remained statistically significant. The sensitivity analysis was included in the leavepiece.

The Appeal Board considered that the leavepiece was not inconsistent with the study authors' comments about the differences between Actonel and alendronate. NHS resources were not referred to. Although the absolute difference was small, a statistically significant difference between the two products had been identified in favour of Actonel. The Appeal Board noted the complainant's comments about scientific rigour and observational studies. The Appeal Board noted the companies' submission that such studies provided a measure of effectiveness across a range of patients and health practices. The Appeal Board noted that observational studies did not measure efficacy. They might nonetheless be used to complement clinical decisions. The Appeal Board also noted the submission that the products were suitable subjects for an observational study as their licensed indications were similar and the baseline characteristics of the two study cohorts were similar.

Taking all the factors into account the Appeal Board did not consider that the leavepiece was misleading and thus ruled no breach of the Code.

An anonymous consultant physician with a specialist interest in metabolic bone disease complained about a leavepiece (ref ACT 3356/IE.RIS.06.12.02) for Actonel (risedronate sodium) issued by Sanofi-Aventis and Procter & Gamble Pharmaceuticals UK Limited, as the Alliance for Better Bone Health (ABBH).

COMPLAINT

The complainant stated that for the last decade he had been responsible for development of osteoporosis services within his trust to provide local general practice with bone densitometry and expert opinion on management issues. Tragically, the plight of the frail elderly had attracted little material prioritisation from the Department of Health (DoH) resulting in patients and generalists alike coming to disproportionately rely upon the activities of enthusiasts such as himself.

Throughout his career, the complainant had enjoyed a constructive relationship with the pharmaceutical industry and indeed the industry had contributed substantially to progress in the management of osteoporosis both in terms of therapeutics and with regard to medical education. The complainant stated that he was thus saddened that he felt compelled to complain about an example of very poor judgement. The leavepiece at issue referred to Silverman *et al* (2007) (the risedronate and alendronate (REAL) cohort study) and drew inferences regarding the comparative efficacy of the two agents. The leavepiece contended that the REAL study unequivocally demonstrated a significant benefit in terms of hip fracture reduction for Actonel relative to the generically available alendronate.

Observational cohort studies certainly served a purpose in an appropriate context. However, given the plethora of well conducted, randomized, controlled, osteoporosis trials available for critical appraisal, the complainant took issue with the selective conclusions in the leavepiece. Single-patient, meta-analysis of results informed by randomized, controlled trials resided at the pinnacle of the evidence hierarchy. In the absence of such data, reliance on evidence obtained from observational studies was probably reasonable. That was clearly not the case in this situation.

A substantial body of evidence concerning the efficacy of anti-fracture medicines including Actonel and alendronate suggested fracture rates, including hip fracture, might be halved during three years of therapy. No randomized, controlled trial had demonstrated differential anti-fracture efficacy for the two products in question. Indeed, comparative studies, that were insufficiently powered to demonstrate differential effects on fracture reduction, had shown superior response in terms of surrogate markers (bone density) for alendronate rather than Actonel.

Perhaps most importantly, current guidelines from the National Institute of Health and Clinical Excellence (NICE) (Health Technology Appraisal 87) did not recognise a difference in terms of the relative efficacy of these products. NICE would imminently update its guidance and also provide recommendations on the primary prevention of osteoporotic fracture in separate

guidance. This guidance was likely at the final Appraisal Consultation Document (ACD) phase and was available on the NICE website. The complainant noted that the current draft of the ACD recommended alendronate as first line treatment for postmenopausal osteoporosis and explicitly did not recommend Actonel as appropriate use of NHS resources. Whilst this was draft guidance, and therefore not to be relied upon per se, the rationale for NICE's prioritisation of alendronate was contingent upon the substantial difference in price between the two; alendronate had been available generically in the UK for almost two years and had a Drug Tariff price of £7.22 compared with £20.30 for weekly Actonel.

The results of the pharmacoeconomic analysis conducted by NICE for two probably similarly efficacious products, predictably, and correctly in the complainant's view, dominated for alendronate over Actonel in all modelling scenarios.

Thus was the central tenet of the complaint. The REAL study did not represent the substantial evidence base derived for Actonel and alendronate. Furthermore, the complainant considered that the inappropriately aggressive (and inaccurate) conclusions presented within the leavepiece attempted to dissuade practitioners from using alendronate in preference to Actonel, contrary to current and likely future NICE guidance. Such promotional messages confused practitioners and potentially diverted scant NHS resources to fund non-competitively priced branded medicines that offered no clinical benefit relative to generically available alternatives. The consequence for specialists such as the complainant was very unappealing.

The complainant requested the Authority to compel the ABBH to withdraw the leavepiece and issue a corrective statement to those health professionals exposed to a campaign of mis-information.

When writing to the companies the Authority asked them to bear in mind the requirements of Clauses 7.2 and 7.4 of the Code.

RESPONSE

Procter & Gamble responded on behalf of both companies.

The companies stated that there were no published, randomized, head-to-head, clinical trials of Actonel and alendronate which had the clinically relevant endpoint of fracture. There were some direct comparisons which used the surrogate endpoint of bone mineral density (BMD) changes, but surrogate endpoints in general were not satisfactory as BMD was not a good predictor of fracture risk (Cummings *et al* 2002; Li *et al* 2001; Watts *et al* 2004).

Furthermore, the Code did not require randomized trials to substantiate claims; other types of study were also acceptable depending on the claim in question.

The REAL cohort study was an observational study. Such studies provided a measure of effectiveness across a range of patients and health care practices as they extended the knowledge of randomized, controlled trials (RCTs).

RCTs by design had strict inclusion and exclusion criteria. It had been shown that approximately 80% of patients would not be accepted into clinical trials for numerous reasons (Dowd *et al* 2000). Therefore RCTs excluded a large number of patients for whom medical professionals would consider treatment in daily practice.

The aim of the REAL study was to observe, in clinical practice, the incidence of hip and nonvertebral fractures among postmenopausal women in the year following initiation of once-weekly Actonel or alendronate.

The Actonel and alendronate groups were compared for baseline characteristics for six months prior to starting bisphosphonate therapy and were of very similar age, comorbidities, and fracture history before therapy. For the first three months of therapy, the two groups had nearly identical fracture rates – which suggested a similarity in fracture risk before the effect of therapy began. The Actonel group could be considered slightly less healthy and at slightly greater risk of fracture based on statistically significant differences in things like concomitant medications, steroid usage, osteoporosis diagnoses, and rheumatoid arthritis diagnosis, however, all results were risk-adjusted for potential differences in baseline fracture risk with standard statistical methods.

In this observational study of women 65 and older, at 6 months Actonel patients had a 46% (p=0.02) lower incidence of hip fractures and a 19% (p=0.05) lower incidence of nonvertebral (hip, wrists, humerus, clavicle, pelvis and leg) fractures, than those on alendronate. At 12 months, Actonel patients had a 43% (p=0.01) lower incidence of hip fractures and an 18% (p=0.03) lower incidence of nonvertebral fractures than patients on alendronate.

There was no opportunity for manipulation – all five of the authors were involved in the development of the study plan, had access to all of the data, and each of the statisticians completed independent analysis. The analysis for this study was performed independently by all authors to ensure no errors or misinterpretations.

The REAL study had been published in the peer reviewed medical journal Osteoporosis International and provided medical professionals with new information on osteoporotic therapies in a real-life setting which had not been observed before and which complemented the finding of the Actonel RCTs as shown in the copy. The leavepiece clearly stated the study description, shared details of the statistical analysis and accurately represented the study findings. The data in the leavepiece was a direct representation of the data in the published paper. The companies believed the data presented were accurate, capable of substantiation and did not mislead physicians

especially in regard to the use of NHS resources as noted by the complainant. The companies noted that current NICE guidelines recommended bisphosphonates (alendronate, etidronate, Actonel) as first line options, and this was what NHS practitioners should base their decisions on today.

The complaint was based on pure speculation of future discussions and future NICE guidelines and furthermore, the complainant specifically referred to NICE pharmacoeconomic analyses – these were not the same as real life clinical outcome data as presented in the REAL study, so in effect the complainant was comparing apples and pears.

There was no obligation to replicate the views of NICE in promotion. Promotion must be within licence with claims in line with the summary of product characteristics (SPC) and capable of substantiation – all of which criteria were met in the leavepiece in question.

The companies therefore, denied any breach of the Code.

PANEL RULING

The Panel noted that there were differences in the indications for Actonel and Fosamax. In the UK Actonel Once Weekly was indicated for the treatment of established postmenopausal osteoporosis to reduce the risk of hip fractures as well as for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral fracture. Whereas Fosamax Once Weekly was indicated for the 'Treatment of postmenopausal osteoporosis, 'Fosamax' reduces the risk of vertebral and hip fractures'.

The Panel noted that the leavepiece at issue was headed 'In established postmenopausal osteoporosis' and referred to the REAL study which had been sponsored by the ABBH. The study had been conducted in the US and was a retrospective observation of bisphosphonate patients which compared the annual incidence of fracture with either once-weekly 35mg Actonel (n=12,215) or once-weekly alendronate (n=21,615). Women for inclusion were aged 65 and over with any use of once-a-week dosing of Actonel or alendronate after July 2002 (when once-weekly versions of both therapies became available). The Panel noted that 8% of the alendronate patients received only 35mg weekly compared with 70mg weekly which was the dose licensed in the UK for the treatment of postmenopausal osteoporosis. Page 2 of the leavepiece presented a comparison of the incidence of hip fracture during therapy at 6 and 12 months. The percentage of women with a hip fracture on alendronate was 0.29% and 0.58% at 6 and 12 months respectively. The percentage of women with a hip fracture on Actonel was 0.17% and 0.37% at 6 and 12 months respectively; an absolute difference of 0.12% (p=0.02) and 0.21% (p=0.01) respectively. In that regard the Panel queried the clinical significance of the results. The relative reductions for patients on Actonel were 46% and 43% at 6 and 12 months respectively. The leavepiece presented that data in a bar chart which noted the absolute percentages of women with a hip fracture together with prominent downward arrows showing the relative differences of 46% and 43% at 3 and 6 months respectively. Below the bar chart was the claim 'Actonel reduces the incidence of hip fracture compared to alendronate as early as 6 months in real life'.

The REAL study concluded that, 'within this observational study of clinical practice, a cohort of patients receiving risedronate had lower rates of hip and nonvertebral fractures during their first year of therapy than a cohort of patients receiving alendronate. These results do not appear to be explained by baseline differences in fracture risk between cohorts. In addition, the observed rates of fracture were consistent with the fracture rates in clinical trials. Thus it appears, patients receiving risedronate are better protected from hip and nonvertebral fractures during their first year of therapy than patients receiving alendronate'.

The Panel considered that the leavepiece was more positive about the differences between Actonel and alendronate than the study authors. In that regard, although NHS resources were not referred to per se, the leavepiece encouraged the use of Actonel and not alendronate. Although a statistically significant difference between the two products had been identified in favour of Actonel, the absolute difference was small. Furthermore the results might have been biased against alendronate given that 8% of the alendronate patients had only received half the weekly dose licensed for the treatment of established postmenopausal osteoporosis ie 35mg vs 70mg.

Taking all the factors into consideration the Panel considered that the leavepiece was misleading and thus ruled breaches of Clauses 7.2 and 7.4. This ruling was appealed by Procter & Gamble and Sanofi-Aventis.

APPEAL BY PROCTER & GAMBLE AND SANOFI-AVENTIS

The ABBH noted that the Panel had noted that 8% (n=1768) of the alendronate patients received 35mg weekly (licensed in the US for prevention of postmenopausal osteoporosis) compared to 92% who received 70mg weekly (licensed in the UK for the treatment of postmenopausal osteoporosis). The Panel was concerned that this 8% of the population might have biased the results against alendronate.

The ABBH submitted that the authors considered this point and performed a sensitivity analysis that proved that the overall results were not affected by groups that could have introduced potential bias, eg the 8% of patients taking 35mg alendronate. As part of the overall sensitivity analysis the authors removed the patients who took alendronate 35mg from the study population and reanalysed the data. The results were similar to the main study, remaining statistically significant and were presented in the publication and the leavepiece in question. The ABBH therefore had confidence in the robustness of the overall study

results due to the consistent results of the sensitivity analysis.

The ABBH noted that the Panel ruling had noted that the percentage of women with a hip fracture who took alendronate was 0.29% and 0.58% at 6 and 12 months, respectively. The percentage of women with a hip fracture who took Actonel was 0.17% and 0.37% at 6 and 12 months, respectively. The Panel was concerned that whilst the difference between the groups was statistically significant, the absolute percentage difference was small (0.12% and 0.21% at 6 and 12 months, respectively) and queried the clinical significance.

The ABBH submitted that there were three points to consider: the need for observational data; consistency of the REAL data compared to clinical trials demonstrating reliability and clinical significance of the results.

The ABBH submitted that health professionals looked to make comparisons of active treatments with clinically relevant endpoints such as fractures in the case of osteoporosis. Often this could only be done by relying on individual trial data as head-to-head trials were not feasible.

As the incidence of hip fractures in the general population was low, it would not be realistic to perform a head-to-head clinical trial with hip fracture as a primary endpoint. In order to show a statistically significant difference in hip fracture incidence between two active treatments in a clinical trial, it would require screening more than 150,000 patients in order to enrol the required number of patients to show a difference, ie 30,000. This was based on feasibility studies that showed only 20% of osteoporotic patients might be eligible for inclusion in randomised controlled trials due to the strict inclusion/exclusion criteria (Dowd et al).

In order to perform such comparative analyses other sources of data, such as health databases for retrospective analyses could be looked at. Such databases contained large volumes of data and allowed screening of large numbers of patients for possible inclusion in such cohort analyses. Thus in the REAL study, 182,772 patients were screened and the analysis included 33,830 patients.

The authors stated 'In the current study, the annual fracture rates following initiation of therapy (~2.0% for nonvertebral fractures and ~ 0.5% for hip fractures) were consistent with the annual rates in the treated population of clinical trials (between 2.0 and 2.3% for non-vertebral fractures and **between 0.4% and 0.7% for hip fractures**)' [emphasis added]. This meant that the fracture incidences observed in the REAL study at 12 months, 0.37% and 0.58% for risedronate and alendronate, respectively, were comparable to those clinical trials.

Fundamentally, it was important to note that the REAL study compared two active cohorts, ie there was no placebo group. This could be highlighted as the magnitude of treatment effect between active comparators was, as expected, lower than between treatment and placebo.

In the UK in 2006, approximately 766,554 patients were taking a bisphosphonate (IMS Data, March 2007). If it was assumed that all were taking alendronate, from the REAL study, 0.58% would experience a hip fracture by 12 months, ie 4,446 hip fractures. If it was assumed that all patients were taking risedronate, 0.37% would experience a hip fracture by 12 months, ie 2,836 hip fractures. The difference was 1,610 hip fractures. Considering the impact hip fractures had on mortality and the patient's quality of life, the clinical significance of this study should not be underestimated. The results were clinically relevant.

The ABBH noted that the Panel noted the conclusion of the study 'Within this observational study of clinical practice, a cohort of patients receiving risedronate had lower rates of hip and nonvertebral fractures during their first year of therapy than a cohort of patients receiving alendronate. These results do not appear to be explained by baseline differences in fracture risk between cohorts. In addition, the observed rates of fracture were consistent with the fracture rates in clinical trials. Thus it appears patients receiving risedronate were better protected from hip and nonvertebral fractures during the first year of therapy than patients receiving alendronate'.

The ABBH submitted that it had addressed the main points in relation to the conclusion of the study, ie the potential bias due to use of 8% alendronate patients on 35mg/week dose and the clinical significance of the data. The ABBH considered that it included all relevant data in the leavepiece, where details and methods of the statistical analysis were clearly presented, including details of the sensitivity analysis which showed that inclusion of the 8% of patients taking alendronate 35mg/weekly did not influence the overall results of the REAL study. Therefore, the overall results presented in the paper were fairly reflected in the leavepiece.

COMMENTS FROM THE COMPLAINANT

The complainant stated that his intention in complaining was to highlight inappropriate and frankly misrepresentative marketing activities perpetrated by the ABBH. Every health professional currently operating within the NHS was subject to tremendous cost containment pressure. Accordingly, promotional campaigns that could result in mis-allocation of overstretched budgets to acquire non-competitively priced products or devices were simply unacceptable and must be curtailed.

The complainant alleged that the key issue was that evidence-based conclusions could only be derived from the outcomes of appropriately designed, randomised controlled clinical studies of adequate duration undertaken in a study population that was representative of those patients likely to be treated in clinical practice once the medicine had been granted

marketing approval. Observational studies inherently lacked the requisite scientific rigour to provide definitive conclusions of relative efficacy of pharmacological agents. It was neither the gift nor capability of pharmaceutical company marketeers to usurp this globally ratified hierarchical approach that had become central to rational clinical decision making and allocation of health resources.

The complainant noted that the companies stated that this complaint was based upon speculation and future NICE guidance, and furthermore, that the analysis was trying to compare apples with pears. The current NICE Technology Appraisal (TA87) did indeed place alendronate and risedronate on an equal footing. The pharmacoeconomic analyses that informed the current NICE Technology Appraisal were based upon acquisition costs of £23.12 for alendronate (4 weekly tablets) and £20.30 for risedronate (4 weekly tablets). It was not speculation to state that the current price of generic alendronate had reduced by 72% to £6.46 for 4 weeks' supply; during the same time frame the price of risedronate had reduced by 7% from £21.83 to £20.30 for 4 weeks' supply. That was a fact; and was naturally the particular fact that had informed the imminent revision of the current NICE Technology Appraisal which would likely place alendronate as the first line agent and indicate that risedronate did not represent a rational use of NHS resources. Expressed another way, in respect of local drug budgets, for every patient treated with risedronate, three patients could be treated with alendronate.

The complainant noted that the ABBH had referred to Cummings *et al* to challenge the validity of deriving conclusions on the relative efficacy of two products based upon surrogate endpoints. Whilst the conclusions of that particular paper could be challenged by findings of other investigators (Hochberg *et al* 2002), the complainant concurred that evidence-based conclusions could not be based on studies that failed to compare the relevant clinical outcome ie fracture in this case. However, the complainant disagreed that such fracture end-point studies were infeasible. Given that 310,000 fragility fracture patients presented to UK hospitals every year, the vast majority of which were drug naïve, the UK alone would provide more than enough patients to recruit to the 30,000 patient study required to prove whether Actonel had any advantage over a generic product that was one third of the price. Globally, there were millions of fragility fracture patients presenting to hospitals every year, the vast majority of whom were currently not treated. The lack of feasibility of such study was not attributable to clinical challenges or lack of patient presentation, rather an unwillingness of pharmaceutical complanies to invest in the, albeit, substantial costs to underwrite such a study.

The complainant alleged that on the issue of generalisability of this data to the UK population, the UK and US populations had a number of clinically relevant distinctions in respect of osteoporosis that might challenge the wisdom of application of these findings to the UK. Indeed, the title of a paper in the British Journal of Radiology provided some insight on this matter 'Prevalence of osteoporotic bone mineral density at the hip in Britain differs substantially from the US over 50 years of age; implications for clinical densitometry' (Holt *et al* 2002). Accordingly, notwithstanding the methodological issues with the REAL study, precisely how REAL were these results derived from US patients when applied to ladies in Inverness, Bolton or Plymouth?

The complainant noted that 'Evidence-based medicine has come a long way: the second decade will be as exciting as the first' was the title of a BMJ paper in 2004 from the McMaster University advocates of evidence-based medicine (Guyatt *et al* 2004); and within the UK NHS evidence-based decision making had indeed progressed substantially. Perhaps in this regard the ABBH should listen to its 'clients' a little more closely. Specious and misrepresentative claims such as 'Protect more patients from hip fractures with Actonel compared to alendronate' that were based upon the findings of observational studies were the stuff of the last century and were best left there.

Evidence-based medicine was founded in Britain; the complainant would not stand by and see its principles flaunted at the expense of patients and the taxpayer. The Appeal Board should uphold this complaint and bring the most severe sanctions at its disposal to bear upon those that would subvert scant resources to line corporate coffers.

In response to a request for the provision of Holt *et al* and Hochberg *et al* the complainant made further comment. In regard to Hochberg *et al* the complainant noted he cited it to illustrate the point that two divergent schools of thought existed on this particular matter. Half a dozen publications could be quoted by the adversarial academic groups, however, this paper with associated references illustrated the opposed view to Cummings *et al* cited by the ABBH. The complainant hoped that this served to inform the Appeal Board that interpretation of the bone mineral density response data was somewhat equivocal, as one would imagine in respect of reliance upon a surrogate end-point.

APPEAL BOARD RULING

The Appeal Board noted that the REAL study was a retrospective observation of bisphosphonate patients which compared the annual incidence of fracture with either once-weekly 35mg Actonel (n=12,215) or once-weekly alendronate (n=21,615). Women for inclusion were aged 65 and over with any use of once-a-week dosing of Actonel or alendronate after July 2002 (when once-weekly versions of both therapies became available). The Appeal Board noted that in the REAL study 8% of the alendronate patients received only 35mg weekly compared to 70mg weekly which was the licensed dose in the UK for the treatment of postmenopausal osteoporosis. The REAL study authors had performed a sensitivity analysis whereby the 1,768 patients who received the 35mg alendronate dose were removed from the study population and the data was reanalysed. The ABBH submitted that the result was

consistent with the primary analysis and remained statistically significant. The sensitivity analysis was included in the leavepiece. Page 2 of the leavepiece compared the incidence of hip fracture during therapy at 6 and 12 months. The percentage of women with a hip fracture on alendronate was 0.29% and 0.58% at 6 and 12 months respectively. The percentage of women with a hip fracture on Actonel was 0.17% and 0.37% at 6 and 12 months respectively; an absolute difference of 0.12% (p=0.02) and 0.21% (p=0.01) respectively. The relative reductions for patients on Actonel were 46% and 43% at 6 and 12 months respectively. The leavepiece presented that data in a bar chart which noted the absolute percentages of women with a hip fracture together with prominent downward arrows showing the relative differences of 46% and 43% at 3 and 6 months respectively. Below the bar chart was the claim 'Actonel reduces the incidence of hip fracture compared to alendronate as early as 6 months in real life'.

The REAL study concluded that, 'within this observational study of clinical practice, a cohort of patients receiving risedronate had lower rates of hip and nonvertebral fractures during their first year of therapy than a cohort of patients receiving alendronate. These results do not appear to be explained by baseline differences in fracture risk between cohorts. In addition, the observed rates of fracture were consistent with the fracture rates in clinical trials. Thus it appears, patients receiving risedronate are better protected from hip and nonvertebral fractures during their first year of therapy than patients receiving alendronate'.

The Appeal Board considered that the leavepiece was not inconsistent with the study authors' comments about the differences between Actonel and alendronate. NHS resources were not referred to. Although the absolute difference was small, a statistically significant difference between the two products had been identified in favour of Actonel. The Appeal Board noted the complainant's comments about scientific rigour and observational studies. The Appeal Board noted the companies' submission that such studies provided a measure of effectiveness across a range of patients and health practices. The Appeal Board noted that observational studies did not measure efficacy. They might nonetheless be used to complement clinical decisions. The Appeal Board also noted the company representatives' submission that the products were suitable subjects for an observational study as their licensed indications were similar and the baseline characteristics of the two study cohorts were similar.

Taking all the factors into account the Appeal Board did not consider that the leavepiece was misleading and thus ruled no breach of Clauses 7.2 and 7.4. The appeal was successful.

Complaint received	**28 March 2007**
Case completed	**14 June 2007**