CASE AUTH/1825/4/06

PROSTRAKAN v SHIRE

Calcichew-D_3 Forte journal advertisement

ProStrakan complained about a journal advertisement for Calcichew-D_3 Forte (calcium carbonate, colecalciferol) issued by Shire. The claim at issue, 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise. In a comparative study, Calcichew-D_3 Forte was preferred over Adcal-D_3 by 80% of patients', was referenced to Rees and Howe (2001).

ProStrakan alleged that the claim was unfair and misleading. Calcichew-D_3 Forte was a chewable tablet containing 1250mg calcium carbonate (equivalent to 500mg of elemental calcium) plus 400 IU vitamin D_3. Adcal-D_3 was a chewable tablet containing 1500mg calcium carbonate (equivalent to 600mg of elemental calcium) plus 400 IU cholecalciferol (vitamin D_3). Rees and Howe was a randomised, investigator-blind, crossover, multicentre study of seven days' treatment in 102 patients ≥ 60 years already receiving daily calcium and vitamin D supplements. At the time of recruitment 64% had been established on Calcichew-D_3 Forte; the proportion of patients already on Adcal-D_3 was unknown, although its market share at the time was 4-8%. This was important as the trial was open from the patients' perspective and the tablets were quite different in terms of calcium carbonate content and this could have a significant impact on the results as calcium carbonate contributed the vast majority of the bulk of the tablet. Assessment of preference was determined through the use of a questionnaire using a visual analogue scale. The results were statistically in favour of the Calcichew-D_3 Forte, with a preference of 79.8%. ProStrakan stated that there were no explanations of the rationale for the questions within the study, nor the clinical relevance to the patient as this was a non-standardised questionnaire.

ProStrakan alleged that there might have been statistical differences generated, apparently using a methodology not pre-specified in the protocol, despite this the median values were very similar in most cases, with significant overlap in the range. On closer examination of the results, the questions appeared biased against a tablet containing more calcium carbonate eg chalky and gritty. This would naturally bias the study against Adcal-D_3.

Currently there were two other combination supplements on the market, Cacit D3 (calcium 1250mg, vitamin D_3 440 IU) and Calceos (calcium 1250mg, vitamin D_3 440 IU), which were the same dose as Calcichew-D_3 Forte. For a taste preference study to be fair a comparison between brands with the same constitution would seem fair.

In addition ProStrakan alleged that the claim would mislead readers into believing that preferred was not quantified, which could potentially lead the reader to believe that there was a compliance difference between the products, data for which had not been provided.

ProStrakan alleged that this unfair comparison of Adcal-D_3 and Calcichew-D_3 Forte was of significant importance clinically, as a substantial body of evidence demonstrated a clinical benefit for a 1200mg dose of calcium carbonate (Adcal-D_3) compared with a 1000mg dose (Calcichew-D_3 Forte). This was misleading as the two products were not comparable and the claim was out of context. The relevant clinical papers and a review of this data were provided for context.

Section 5.1 of the Adcal-D_3 summary of product characteristics (SPC) further reinforced the differences which stated that there was strong evidence that supplemental calcium and vitamin D_3 could reduce the incidence of hip and other non-vertebral fractures. In a randomised placebo controlled study, 3270 patients treated with 1200mg elemental calcium and 800 IU vitamin D_3 daily, ie, the same dose delivered by two tablets of Adcal-D_3, the number of hip fractures was 43% lower (p=0.043) and the total number of non-vertebral fractures was 32% lower than among those who received placebo. A positive effect on bone mineral density was also observed. The Calcichew-D_3 Forte SPC contained the same data (Chapuy *et al*) stating the important dose was 1200mg/day of elemental calcium.

ProStrakan alleged that Rees and Howe and the subsequent claims were unfair and misleading, as the two products were not comparable in outcomes or dosing and the claim was out of context.

The Panel noted that the aim of Rees and Howe was to compare the acceptability of Calcichew-D_3 Forte with Adacal-D_3. Both products had similar

indications and although they had different constituents the Panel considered that it was not unreasonable to compare the two. Patients (n=102) took Calcichew-D_3 for seven days followed by Adcal-D_3 for seven days or vice versa. At the end of each study period patients used visual analogue scales to indicate palatability in terms of grittiness, chalkiness, taste (bitter or sweet), ease of chewing, ease of swallowing and stickiness of each product; there was no difference between the two with regard to taste. The five other parameters were statistically significantly in favour of Calcichew-D_3 Forte. After the second study period patients were asked which treatment they preferred.

The Panel considered that most readers of the advertisement would assume that 80% of patients preferred Calcichew-D_3 Forte to Adacal-D_3 because they thought it tasted better. Women in the advertisement were pictured with a smile, the claim was positioned next to their mouth and the product logo incorporated a picture of lemons. In Rees and Howe, however, patients were asked to assess palatability in terms of grittiness, chalkiness, ease of chewing, swallowing and stickiness on teeth as well as taste. The Panel considered that the patients' views on these other parameters had influenced their preference given that there was no difference between the two as to perception of taste.

The Panel queried whether the seven day treatment periods were long enough to assess medicines that were intended for long term use. All patients recruited into the study were already taking calcium supplements; 64% of them were established on Calcichew-D_3 Forte.

The Panel was concerned that insufficient detail was given about what it was that patients preferred about treatment with Calcichew-D_3 Forte compared to treatment with Adcal-D_3. The claim implied that not only did patients prefer Calcichew-D_3 Forte to Adcal-D_3 but they also found it pleasant to take. There was no data in that regard.

The Panel disagreed with Shire's view that the data on efficacy evaluations and health economics were irrelevant to the current complaint which only dealt with the issue of patient preference. The Panel considered that in addition to palatability a patient's knowledge of some of the efficacy evaluations and differences in clinical outcomes between two products might affect their preference for one or the other. Without such knowledge patients would be unable to express a genuine, well informed preference.

Overall the Panel considered that the claim at issue, 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise. In a comparative study, Calcichew-D_3 Forte was preferred over Adcal-D_3 by 80% of patients', was a misleading comparison. Thus the Panel ruled breaches of the Code.

ProStrakan Group Plc complained about an advertisement (ref 003/0419a) for Calcichew-D_3 Forte (calcium carbonate, colecalciferol) issued by Shire Pharmaceuticals Ltd which appeared in Pulse, 2 March 2006. The claim at issue, 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise. In a comparative study, Calcichew-D_3 Forte was preferred over Adcal-D_3 by 80% of patients', was referenced to Rees and Howe (2001).

Calcichew-D_3 Forte was indicated for the treatment and prevention of vitamin D/calcium deficiency (characterised by raised serum alkaline phosphatase levels associated with increased bone loss, raised levels of serum PTH and lowered 25-hydroxyvitamin D) particularly in the housebound and institutionalised elderly subjects. It was also indicated for the supplementation of vitamin D and calcium as an adjunct to specific therapy for osteoporosis, in pregnancy, in established vitamin D dependent osteomalacia, and in other situations requiring therapeutic supplementation of malnutrition.

ProStrakan marketed Adcal-D_3 which was indicated as an adjunct to specific therapy for osteoporosis and in situations requiring therapeutic supplementation of malnutrition eg in pregnancy and established vitamin D dependent osteomalacia. It was also indicated for the prevention and treatment of calcium deficiency/vitamin D deficiency especially in the housebound and institutionalised elderly subjects. Deficiency of the active moieties was indicated by raised levels of PTH, lowered 25-hydroxy vitamin D and raised alkaline phosphatase levels which were associated with increased bone loss.

COMPLAINT

ProStrakan alleged that the claim was unfair and misleading. Calcichew-D_3 Forte was a chewable tablet containing 1250mg calcium carbonate (equivalent to 500mg of elemental calcium) plus 400 IU vitamin D_3. Adcal-D_3 was a chewable tablet containing 1500mg calcium carbonate PhEur (equivalent to 600mg of elemental calcium) plus 400 IU cholecalciferol (vitamin D_3). Rees and Howe was a randomised, investigator-blind, crossover, multicentre study of seven days' treatment in 102 patients ≥ 60 years already receiving daily calcium and vitamin D supplements as part of their routine management. At the time of recruitment 64% had been established on Calcichew-D_3 Forte; the proportion of patients already on Adcal-D_3 was unknown although its market share at the time was 4-8%. This was important as the trial was open from the patients' perspective and the tablets were quite different in terms of calcium carbonate content (12.5% more in Adcal-D_3). This could have a significant impact on the results (in addition to the significant clinical outcomes delivered by the different doses), as calcium carbonate contributed the vast majority of the bulk of the tablet. The comparison groups were well balanced at baseline. Assessment of preference was determined through the use of a questionnaire assessed using a visual analogue scale designed specifically for this trial. The results were statistically in favour of the Calcichew-D_3 Forte, with a preference of 79.8%.

ProStrakan stated that there were no explanations of the rationale for the questions within the study, nor the clinical relevance to the patient as this was a non-standardised questionnaire. ProStrakan alleged that there might have been statistical differences

generated, apparently using a methodology not pre-specified in the protocol, despite this the median values were very similar in most cases, with significant overlap in the range. On closer examination of the results, the questions appeared biased against a tablet containing more calcium carbonate eg chalky and gritty. This would naturally bias the study against Adcal-D_3.

ProStrakan noted that currently there were two other combination supplements on the market, Cacit D3 (calcium 1250mg, vitamin D_3 440 IU) and Calceos (calcium 1250mg, vitamin D_3 440 IU), which were the same dose as Calcichew-D_3 Forte. For a taste preference study to be fair a comparison between brands with the same constitution would seem fair.

In addition ProStrakan alleged that this claim would mislead readers into believing that preferred was not quantified, which could potentially lead the reader to believe that there was a compliance difference between the products, data for which had not been provided.

ProStrakan alleged that this unfair comparison of Adcal-D_3 and Calcichew-D_3 Forte was of significant importance clinically, as a substantial body of evidence demonstrated a clinical benefit for a 1200mg (Adcal-D_3) compared with a 1000mg dose (Calcichew-D_3 Forte). This was misleading as the two products were not comparable and the claim was out of context. The relevant clinical papers and a review of this data were provided for context.

Chapuy *et al* (1992) was a double-blind placebo controlled randomised trial of 3270 participants in which interim analysis had demonstrated that hip fracture rate was 43% lower (p=0.043), total non-vertebral fractures 32% lower (p=0.015) in the calcium (1200mg)/vitamin D3 (800 IU) group compared to placebo. These results were further reinforced by Chapuy *et al* (2004), in which the results from the end of the 36 months confirmed that non-vertebral fractures were significantly less than placebo ($p<0.01$) as well as hip fractures ($p<0.01$).

ProStrakan further stated that these results were reinforced in Chapuy *et al* (2002) on an at risk population. These data agreed with those from previous studies and indicated that 1200mg of elemental calcium and vitamin D_3 800 IU in combination reversed senile secondary hyperparathyroidism and reduced both hip bone loss and the risk of hip fracture in elderly institutionalised women.

ProStrakan stated that a pharmacoeconomic review of the (elemental) 1200mg calcium and vitamin D 800 IU data, covering seven European countries by Lilliu *et al* (2003) had demonstrated that the supplementation strategy was cost saving with this dose, estimated to be 79,000 – 711,000 Euro per 1000 women.

ProStrakan alleged that the significant body of evidence generated for 1000mg of calcium combined with vitamin D_3 800 IU (Porthouse *et al* 2005, Grant *et al* 2005 and Deroisy *et al* 1998), failed to show the clinically significant reductions in clinically relevant endpoints.

ProStrakan noted that further studies had examined the impact of 1000mg elemental calcium combination vs separate 1200mg calcium and vitamin D. Deroisy *et al* was a one year, open-label, randomised prospective study of two parallel groups in 119 patients. ProStrakan alleged that that this study was methodologically poor with several design flaws, leading to a significant difference in compliance to treatment. This had led to confusing and inconsistent results, with no evidence of equal clinical efficacy.

This large and significant body of evidence suggested that 1000mg of elemental calcium with at least 800 IU vitamin D had a positive effect on bone mineral density (BMD) (Chapuy *et al*, Porthouse *et al*, Grant *et al* and Deroisy *et al*), although there was no significant evidence for clinically and health service relevant outcomes.

ProStrakan noted that Section 5.1 of the Adcal-D_3 SPC further reinforced the differences which stated that there was strong evidence that supplemental calcium and vitamin D_3 could reduce the incidence of hip and other non-vertebral fractures. In a randomised placebo controlled study, 3270 patients treated with 1200mg elemental calcium and 800 IU vitamin D_3 daily, ie, the same dose delivered by two tablets of Adcal-D_3, the number of hip fractures was 43% lower (p=0.043) and the total number of non-vertebral fractures was 32% lower than among those who received placebo. A positive effect on bone mineral density was also observed.

ProStrakan noted that the Calcichew-D_3 Forte SPC contained the same data (Chapuy *et al*) stating the important dose was 1200mg/day of elemental calcium.

ProStrakan alleged that Rees and Howe and the subsequent claims were unfair and misleading, as the two products were not comparable in outcomes or dosing and the claim was out of context and in breach of Clauses 7.2 and 7.3.

RESPONSE

Shire stated that following earlier discussions with ProStrakan, it had agreed on 31 March 2006 to withdraw the advertisement from circulation as soon as was feasible. In particular, Shire agreed to withdraw use of the terms 'Ten Second Trial' and 'Surprisingly Good' which appeared on the second page of the advertisement from future promotional pieces.

Shire submitted that the only point of contention remained the use of material from the comparative palatability and preference study (Rees and Howe), which was justifiable. The emphasis of the complaint concerned the sentence: 'In a comparative study, Calcichew-D_3 Forte was preferred over Adcal-D_3 by 80% of patients'. This study was conducted by an independent clinical research organisation. Shire had not influenced the conduct of the study; Shire's medical director appeared as a co-author only because Shire sponsored the study. This was normal practice and in no way implied any influence on the results by Shire. The study had ethics approval, was conducted in 11 separate GP surgeries and involved 102 patients.

Shire submitted that it was not surprising that 64% of patients had been established on Calcichew-D_3 Forte

as it was the overwhelming market leader at that time. No attempt was made to bias the population in terms of this medicine history. The patients had the clear opportunity to express their preferences and opinions on various palatability parameters, regardless of which product they had previously received. The 64% of patients who had previously received Calcichew-D_3 Forte could have expressed preferences and opinions in favour of Adcal-D_3. The study was of a randomised crossover design to avoid bias and a treatment period on each medicine of seven days was chosen as a reasonable duration in which the patient could form some conclusions about the respective medicines. Inevitably each of the medicines was presented as in the commercial formulation otherwise any conclusions would loose validity.

Shire acknowledged that Adcal-D_3 contained more calcium carbonate than Calcichew-D_3 Forte (20% more, not 12.5% as stated by ProStrakan). The study compared the licensed dosing regimens of the two products. The comparison could not have legitimately been performed in any other way, since one could not break up the tablets. The objective of the study was to compare palatability and preference – not efficacy or safety. Therefore such differences in doses of active constituents were legitimate in the context of this comparison.

Shire submitted that ProStrakan had suggested that the differences in calcium carbonate content of the respective tablets could have a significant impact on the results. The difference was too small for such an inference. In any event, the suggestion provided a reason for an observed difference in preference and differences in palatability of the licensed dosing regimens used in clinical practice. The results in favour of Calcichew-D_3 Forte over Adcal-D_3 reflected the considerable difference between excipients in the two formulations, rather than the small difference in concentrations of one of the active ingredients.

Shire noted that ProStrakan had questioned the rationale for the questions employed in the study. Shire submitted that questions were chosen to investigate palatability differences and preferences between the two products. These comparisons were chosen for the benefit of the patient because of reports from doctors of such differences. The six questions asked on palatability were assessed via the well-established and validated visual analogue scales. The questions were clearly defined in the protocol. The questions were designed to investigate differences between the tablets using obvious features of palatability (grittiness, chalkiness, ease of chewing, ease of swallowing, stickiness, and taste). The p-values for differences in the median visual analogue values for the two products were calculated and quoted.

Shire submitted that it was not clear why ProStrakan raised an issue with palatability questions and answers, since they were not referred to in the advertisement.

Shire submitted that the question on preference was simple and unambiguous; at the end of the 14-day treatment period, the investigator asked the patient:

'Which week's trial treatment did you prefer taking?

Last week's ? This week's ? No preference'

Shire submitted that ProStrakan suggested that the study should have compared Calcichew-D_3 Forte with Cacit D3 or Calceos. There was no reason for Shire to have made such a comparison. There were no reports of poor palatability regarding these products. Incidentally, minimum doses of these two products contained 500mg of calcium – not 1250mg as stated by ProStrakan; and Calceos contained 400 IU (not 440 IU as stated by ProStrakan) of vitamin D. Cacit D3 was presented as a dispersible formulation – which would make palatability comparisons against a Calcichew-D_3 Forte tablet difficult. Further, Cacit D3 contained calcium citrate, not calcium carbonate, as the active calcium source.

Shire noted that ProStrakan had stated that readers might believe that the word 'preferred' was not quantified in the statement 'Calcichew-D_3 Forte was preferred over Adcal-D_3 by 80% of patients'. This statement directly reflected the answer to the simple question specified in the protocol and asked to the patients at the end of the study. Shire submitted that it had been very careful in using this study in its promotional material not to state any compliance advantage for Calcichew-D_3 Forte, as suggested by ProStrakan.

Shire noted that ProStrakan had described at length results from a variety of studies, concentrating on efficacy evaluations and even utilising one health economic argument. Shire submitted that these cited publications were not relevant to the current complaint, which only dealt with the issue of patient preference.

Shire submitted that none of the publications cited by ProStrakan reported results on Adcal-D_3. Published data on Adcal-D_3 (other than those in Rees and Howe) did not exist and ProStrakan had not quoted any Adcal-D_3 studies in its complaint. Some of the publications cited by ProStrakan did not use calcium carbonate (used in Calcichew-D_3 Forte and Adcal-D_3) as the calcium source. For example, calcium phosphate (in sachet formulation) was the active calcium constituent in the 'landmark' Chapuy *et al* study quoted by ProStrakan.

Shire submitted that the comparisons were accurate, balanced, fair, objective and unambiguous. They reflected all the evidence, in that it was not aware of other such comparisons apart from those in the quoted study. The comparisons were not misleading: it was clear that palatability and preference were being compared – not compliance, efficacy or safety. Shire submitted that the cited study had compared medicines intended for the same purpose and compared material, relevant, substantiable and representative features that were important in the practice of clinical medicine. Shire submitted that the claim in question was not in breach of Clauses 7.2 and 7.3 of the Code.

Shire submitted that in conclusion it had merely stated a preference result from a scientifically well-run independent study between licensed doses of two products having the same therapeutic indications.

PANEL RULING

The Panel noted that the aim of Rees and Howe was to compare the acceptability of Calcichew-D_3 Forte with Adacal-D_3. Both products had similar indications and although they had different constituents the Panel considered that it was not unreasonable to compare the two. Patients (n=102) took Calcichew-D_3 for seven days followed by Adcal-D_3 for seven days or vice versa. At the end of each study period patients used visual analogue scales to indicate palatability in terms of grittiness, chalkiness, taste (bitter or sweet), ease of chewing, ease of swallowing and stickiness of each product; there was no difference between the two with regard to taste. The five other parameters were statistically significantly in favour of Calcichew-D_3 Forte. After the second study period patients were asked which treatment they preferred.

The Panel considered that most readers of the advertisement would assume that 80% of patients preferred Calcichew-D_3 Forte to Adacal-D_3 because they thought it tasted better. Women in the advertisement were pictured with a smile, the claim was positioned next to their mouth and the product logo incorporated a picture of lemons. In Rees and Howe, however, patients were asked to assess palatability in terms of grittiness, chalkiness, ease of chewing, swallowing and stickiness on teeth as well as taste. The Panel considered that the patients' views on these other parameters had influenced their preference given that there was no difference between the two as to perception of taste.

The Panel queried whether the seven day treatment periods were long enough to assess medicines that were intended for long term use. All patients recruited into the study were already taking calcium supplements; 64% of them were established on Calcichew-D_3 Forte.

The Panel was concerned that insufficient detail was given about what it was that patients preferred about treatment with Calcichew-D_3 Forte compared to treatment with Adcal-D_3. The claim implied that not only did patients prefer Calcichew-D_3 Forte to Adcal-D_3 but they also found it pleasant to take. There was no data in that regard.

The Panel disagreed with Shire's view that the data on efficacy evaluations and health economics were irrelevant to the current complaint which only dealt with the issue of patient preference. The Panel considered that in addition to palatability a patient's knowledge of some of the efficacy evaluations and differences in clinical outcomes between two products might affect their preference for one or the other. Without such knowledge patients would be unable to express a genuine, well informed preference.

Overall the Panel considered that the claim at issue, 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise. In a comparative study, Calcichew-D_3 Forte was preferred over Adcal-D_3 by 80% of patients', was a misleading comparison. Thus the Panel ruled breaches of Clauses 7.2 and 7.3 of the Code.

Complaint received **7 April 2006**

Case completed **5 June 2006**