Case AUTH/2162/8/08

PROSTRAKAN v GALEN

Promotion of Calceos

ProStrakan complained about a six page, gatefolded leavepiece and a letter to a hospital consultant both issued in support of Calceos (calcium/vitamin D_3) by Galen. ProStrakan supplied Adcal-D_3 (calcium/vitamin D_3).

The leavepiece at issue stated on the front page that 'Calceos is formulated with Taste in mind'. The second page stated that taste was important for patient preference and adherence. The third page gave details of how Calceos was formulated with taste in mind. The fourth page included a cost comparison of Calceos, Adcal-D_3 and Calcichew-D_3 Forte and the fifth (which was adjacent to page 2 when opening the leavepiece) referred to high adherence with calcium and vitamin D_3 supplements doubling the reduction in fracture risk.

The detailed response from Galen is given below.

The claim 'Taste is important for: – Patient preference: – Long-term patient adherence with calcium/vitamin D_3 chewable tablets' appeared on page 2 of the leavepiece; both bullet points were referenced to Reginster *et al* (2005). ProStrakan stated that the study cited measured the preference for, and acceptability of, one tablet and one effervescent powder formulation of calcium and vitamin D_3 supplement. The study did not assess taste in terms of patient preference but rather as part of a set of acceptability criteria. The preference assessment was limited to a simple choice of one formulation over the other. ProStrakan regarded preference and acceptability as fundamentally different and non-interchangeable; preference pertained to the comparison of two or more products whereas acceptability referred to the qualities or properties of a single product. This was how the study assessed the formulations and ProStrakan alleged that the first bullet point regarding taste and preference was misleading, in breach of the Code.

Regarding the second bullet point, Reginster *et al* was conducted over 28 days; this was not long enough to assess 'long-term' adherence, particularly in view of the long extent of treatment in calcium/vitamin D_3 supplementation. Additionally, the authors stated that taste might have an impact, but the leavepiece made a categorical statement. ProStrakan therefore alleged that the second bullet point was also misleading, in breach of the Code.

Reginster *et al* compared the preference and acceptability of a chewable tablet containing the same active ingredients as Calceos and an effervescent formulation. This was important when considering further claims.

The Panel considered that, upon reading the claim at issue, most readers would assume that Reginster *et al* had shown that patients preferred Calceos because of its taste and for that reason would adhere to long-term therapy. This was not so. Reginster *et al* compared Steovit D_3 (chewable tablet) and Calcit D_3 (effervescent powder). Patients completed a widely accepted (but not validated) 11 point rating scale which included 5 acceptability variables; taking the dose, time spent taking the dose, taking the dose out of the container, general convenience of taking the dose and taste. 72.5% of patients preferred the chewable tablet, 19.1% preferred the effervescent powder and 8.4% had no preference (both $p<0.001$ vs tablet). The preference for the tablet was based on consistently and significantly higher mean scores on all 5 variables of acceptability (all $p<0.001$).

The Panel noted that in the study patients had preferred Steovit D_3 to Calcit D_3. The active ingredients of Steovit D_3 were the same as Calceos ie calcium carbonate 1250mg and vitamin D_3 400IU, however it was likely that the tablet excipients, which would contribute to the taste, were not the same. There had been no assessment of the preference for, or the acceptability of Calceos. Although the claim at issue did not mention Calceos, in the context of a Calceos leavepiece, readers would assume that the study cited had included Calceos; the failure to make clear that it did not was misleading.

Reginster *et al* assessed taste as one aspect of acceptability not as the sole reason for patient preference as implied in the leavepiece. In that regard, the claim that taste was important for patient preference was misleading in breach of the Code.

The claim that taste was important for long-term patient adherence did not make clear that the study cited in support had lasted for 28 days only. The authors stated that based on the results of previous studies acceptability and preference might influence long-term compliance. They added that the long-term effects of acceptability of the two formulations were beyond the scope of their study and whether similar results could be found in long-term treatment periods should be the subject of future studies. The Panel thus considered that the claim at issue was misleading and a breach of the Code was ruled.

The claim 'The additive effect of xylitol and sorbitol enhances the lemon flavour of Calceos' appeared on page three of the leavepiece and was referenced to the Calceos summary of product characteristics

(SPC) and the Handbook of Pharmaceutical Excipients (2006). ProStrakan stated that the references cited did not support the claim. The Calceos SPC contained no information regarding the flavour-enhancing properties of either xylitol or sorbitol, The Handbook of Pharmaceutical Excipients stated '…xylitol…is highly effective in enhancing the flavour of tablets…' but had no similar information regarding sorbitol's qualities as a flavour enhancer, referring only to sorbitol's '…pleasant, sweet taste…'. Additionally, the handbook contained no information concerning any additive flavour-enhancing effect of xylitol and sorbitol when combined together in a single formulation. ProStrakan therefore alleged that the claim was misleading. Additionally, the claim that xylitol and sorbitol acted synergistically to enhance the flavour of Calceos could not be substantiated.

The Panel noted Galen's submission that the word 'additive' might be misconstrued and an alternative would be used in future. The Panel, however, remained unsure as to how the references cited supported the claim with regard to enhancing the lemon flavour *per se* of Calceos. The Panel considered that to cite the SPC and Handbook of Pharmaceutical Excipients in support of the claim was misleading and they did not substantiate the claim. No other material was provided. Breaches of the Code were ruled.

A page headed 'Taste the NEW savings with Calceos' was followed by a table comparing the cost of calcium/vitamin D_3 supplements (Calceos, Adcal-D_3 and Calcichew-D_3 Forte).

ProStrakan stated that it was important to consider the previous pages in context with this page which compared Calceos with Adcal-D_3 and Calcichew-D_3 Forte. The central theme hereto was that taste was an important determinant of success in calcium/vitamin D_3 supplementation and that Calceos had unique advantages in terms of taste.

Reginster *et al* did not compare Calceos with other chewable tablets, but rather compared a tablet with similar active ingredients to Calceos with an effervescent tablet. The previous two pages of claims, which had been constructed in a misleading fashion and were largely unsubstantiated by the references cited, would lead the reader to conclude that other calcium/vitamin D_3 supplements should be replaced by Calceos which tasted better and therefore would have better patient adherence rates. The leavepiece in fact contained no data concerning the taste, preference, acceptability or adherence of Calceos either alone or in comparison with either Adcal-D_3 or Calcichew-D_3 Forte. To refer to Adcal-D_3 and Calcichew-D_3 Forte in a leavepiece whose central theme was taste was therefore misleading.

The Panel noted that the leavepiece made a number of claims for taste advantages for Calceos. The context of the cost comparison was an important consideration. The use of the word 'Taste' in the heading to the cost comparison extended this theme and might be read as implying that Calceos had taste advantages over Adcal-D_3 and Calcichew-D_3 Forte. The Panel considered that on balance this implication was misleading and a breach of the Code was ruled.

The claim 'High adherence with calcium and vitamin D supplements *doubles* the reduction in fracture risk' was a heading to a bar chart showing the % reduction of fracture risk for ≥80% adherence (24%), 60-69% adherence (8%) and 50-59% adherence (4%). The bar chart was referenced to a meta-analysis by Tang *et al* (2007). The Calceos logo appeared beneath the bar chart.

ProStrakan noted that the Tang *et al* meta-analysis was of 29 trials of calcium, and calcium/vitamin D_3 supplementation. The claim was true. However, the leavepiece contained no data on the adherence of Calceos and it was therefore misleading to associate Calceos with the benefits of high adherence to calcium/vitamin D_3 supplementation. Moreover, in the context of this piece (which misleadingly implied that Calceos had taste and therefore adherence advantages over other products), this claim implied Calceos would deliver greater (perhaps even double) reduction in fracture risk than competitor products. ProStrakan alleged that the claim, in this context, was misleading.

Additionally, none of the eight studies in Tang *et al* used the dose of calcium and vitamin D_3 (1000mg and 800IU) that was present in Calceos. It was therefore misleading to claim increased fracture risk reduction for Calceos using this reference, in a breach of the Code.

Finally, Tang *et al* made clear recommendations about the minimum doses of calcium and vitamin D_3 (1200mg and 800IU respectively) required for best effect. Since Calceos contained only 1000mg of calcium, ProStrakan considered it misleading to refer to Tang *et al*.

The Panel noted that the statement at issue, referenced to Tang *et al*, claimed that high adherence with calcium and vitamin D_3 supplements would double the reduction in fracture risk. It also included the Calceos logo and appeared immediately on turning the front page which claimed 'Calceos is formulated with Taste in mind' and opposite page 2 which read 'Taste is important for: … Long-term patient adherence with calcium/vitamin D chewable tablets'. The claim would be read as applying to Calceos ie that high adherence with Calceos had been shown to double the reduction in fracture risk. This was not so.

None of the studies in Tang *et al* used the Calceos dose (ie a fixed combination of calcium 1000mg and vitamin D_3 800IU). Thus the Panel considered that in the context in which they appeared the bar chart from Tang *et al* and the claim were misleading; the claim had not been substantiated. Breaches of the Code were ruled.

ProStrakan stated that the letter to a hospital consultant, signed by an employee of Galen, contained information regarding Calceos and cited Tang *et al*. As discussed above, ProStrakan believed this was misleading, as Tang *et al* recommended a dose of calcium that was higher than that contained in Calceos.

The Panel noted that the letter did not refer to any published studies. The Business Case document which accompanied the letter did refer to Tang *et al* but the document did not appear to be the subject of ProStrakan's complaint. There was no reference in the letter to Tang *et al* and no mention of adherence and fracture risk. The Panel ruled no breach of the Code with regard to the allegations made about the letter to the consultant.

ProStrakan complained about the promotion of Calceos (calcium 500mg/vitamin D_3 400IU) by Galen. The materials at issue were a six page, gatefolded leavepiece and a letter to a hospital consultant. ProStrakan supplied Adcal-D_3 (calcium/vitamin D_3). ProStrakan stated that inter-company negotiation had not resolved the matter.

Galen stated that following an internal review the leavepiece was already being withdrawn; ProStrakan would have been informed of this fact had it not moved precipitately to make a formal complaint.

The leavepiece at issue stated on the front page that 'Calceos is formulated with Taste in mind'. The second page stated that taste was important for patient preference and adherence. The third page gave details of how Calceos was formulated with taste in mind. The fourth page included a cost comparison of Calceos, Adcal-D_3 and Calcichew-D_3 Forte and the fifth (which was adjacent to page 2 when opening the leavepiece) referred to high adherence with calcium and vitamin D supplements doubling the reduction in fracture risk.

A Leavepiece

1 Claim 'Taste is important for:
– Patient preference
– Long-term patient adherence with calcium/vitamin D chewable tablets'

This claim appeared on page 2 of the leavepiece; both bullet points were referenced to Reginster *et al* (2005).

COMPLAINT

ProStrakan stated that the study cited measured the preference for, and acceptability of, one tablet and one effervescent powder formulation of calcium and vitamin D_3 supplement. The study did not assess taste in terms of patient preference but rather as part of a set of acceptability criteria. The preference assessment was limited to a simple choice of one formulation over the other.

ProStrakan regarded preference and acceptability as fundamentally different and non-interchangeable in that preference pertained to the comparison of two or more products, whereas acceptability referred to the qualities or properties of a single product. This was how the study assessed the formulations and ProStrakan alleged that the first bullet point regarding taste and preference was misleading, in breach of Clause 7.2.

Regarding the second bullet point, Reginster *et al* was conducted over 28 days; this was not long enough to assess 'long-term' adherence, particularly in view of the long extent of treatment in calcium/vitamin D_3 supplementation. Additionally, the authors stated that taste might have an impact, but the leavepiece made a categorical statement. ProStrakan therefore alleged that the second bullet point was also misleading, in breach of Clause 7.2.

Reginster *et al* compared the preference and acceptability of a chewable tablet containing the same active ingredients as Calceos and an effervescent formulation. This was important when considering further claims.

RESPONSE

Galen stated that the fact that Reginster *et al* compared an oral and effervescent formulation of calcium/vitamin D_3 was not of any relevance as no claims were made regarding the potential advantages of one formulation over another.

Taste was assessed as part of the study. In the penultimate paragraph of the discussion the authors commented:

> 'Marriott and Rees and Howe found that the acceptability of taste is related to product preference and willingness to continue treatment on a long-term basis. For optimal compliance, the taste, size and administration formulation of oral preparations should be acceptable and convenient. Based on the results of the previously mentioned studies, acceptability and preference of any dietary supplement containing calcium and vitamin D_3 may influence compliance in the long term.'

Galen believed that the statements in the leavepiece were a reasonable interpretation of the available data and accordingly not misleading or in breach of Clause 7.2

PANEL RULING

The Panel considered that, upon reading the claim at issue, most readers would assume that Reginster *et al* had shown that patients preferred Calceos because of its taste and for that reason would adhere to long-term therapy. This was not so. The two products Reginster *et al* compared were Steovit

D_3 (chewable tablet) and Calcit D_3 (effervescent powder). Patients completed a widely accepted (but not validated) 11 point rating scale which included 5 acceptability variables; taking the dose, time spent taking the dose, taking the dose out of the container, general convenience of taking the dose and taste. 72.5% of patients preferred the chewable tablet, 19.1% preferred the effervescent powder and 8.4% had no preference (both $p<0.001$ vs tablet). The preference for the tablet was based on consistently and significantly higher mean scores on all 5 variables of acceptability (all $p<0.001$).

The Panel noted that in the study patients had preferred Steovit D_3 to Calcit D_3. The active ingredients of Steovit D_3 were the same as Calceos ie calcium carbonate 1250mg and vitamin D_3 400IU, however it was likely that the tablet excipients, which would contribute to the taste of the products, were not the same. There had been no assessment of the preference for, or the acceptability of Calceos. Although the claim at issue did not mention Calceos, in the context of a Calceos leavepiece, readers would assume that the study cited had included Calceos; the failure to make clear that it did not was misleading.

Reginster *et al* assessed taste as one aspect of acceptability not as the sole reason for patient preference as implied in the leavepiece. In that regard, the claim that taste was important for patient preference was misleading in breach of Clause 7.2.

The claim that taste was important for long-term patient adherence did not make clear that the study cited in support had lasted for 28 days only. The authors stated that based on the results of previous studies acceptability and preference might influence long-term compliance. They added that the long-term effects of acceptability of the two formulations were beyond the scope of their study and whether similar results could be found in long-term treatment periods should be the subject of future studies. The Panel thus considered that the claim at issue was misleading and a breach of Clause 7.2 was ruled.

2 Claim 'The additive effect of xylitol and sorbitol enhances the lemon flavour of Calceos'

This claim appeared on page three of the leavepiece and was referenced to the Calceos summary of product characteristics (SPC) and the Handbook of Pharmaceutical Excipients (2006).

COMPLAINT

ProStrakan stated that the references cited did not support the claim. The Calceos SPC contained no information regarding the flavour-enhancing properties of either xylitol or sorbitol, The Handbook of Pharmaceutical Excipients contained information on xylitol and sorbitol. It stated '…xylitol…is highly effective in enhancing the flavour of tablets…' but had no similar information regarding sorbitol's qualities as a flavour enhancer, referring only to sorbitol's '…pleasant, sweet taste…'. Additionally, the handbook contained no information concerning any additive flavour-enhancing effect of xylitol and sorbitol when combined together in a single formulation. ProStrakan therefore alleged that the claim was misleading, in breach of Clause 7.2. Additionally, ProStrakan did not believe that the claim that xylitol and sorbitol acted synergistically to enhance the flavour of Calceos could be substantiated in breach of Clause 7.4.

RESPONSE

Galen noted that with the Calceos SPC confirmed that xylitol and sorbitol were excipients in the tablet. The Handbook of Pharmaceutical Excipients provided information on the properties and applications of both agents. Xylitol was described as being '….highly effective in enhancing the flavour of tablets and syrups…' and '… can provide chewable tablets with a desirable sweet taste and cooling sensation, without the "chalky" texture experienced with some other tablet diluents'. Sorbitol was described as being '…particularly useful in chewable tablets owing to its pleasant, sweet taste and cooling sensation'.

The word 'additive' referred to the addition of these agents to the tablets rather than meaning a synergistic action of the two agents together. As the word 'additive' might be misconstrued an alternative term would be substituted in future.

However, Galen believed that the references were not misleading, supported the claim and accordingly were not a breach of Clause 7.2 or 7.4.

PANEL RULING

The Panel noted that the claim at issue was referenced to the Calceos SPC and the Handbook of Pharmaceutical Excipients. The Panel noted Galen's submission that the word 'additive' might be misconstrued and an alternative would be used in future. The Panel, however, remained unsure as to how the references cited supported the claim with regard to enhancing the lemon flavour *per se* of Calceos. The Panel considered that to cite the SPC and Handbook of Pharmaceutical Excipients in support of the claim was misleading and they did not substantiate the claim. No other material was provided. Breaches of Clauses 7.2 and 7.4 were ruled.

3 Page headed 'Taste the NEW savings with Calceos'

This was followed by a table comparing the cost of calcium/vitamin D_3 supplements (Calceos, Adcal-D_3 and Calcichew-D_3 Forte).

COMPLAINT

ProStrakan stated that it was important to consider the previous pages in context with this page which compared Calceos with Adcal-D_3 and Calcichew-D_3 Forte. The central theme hereto was that taste was an important determinant of success in calcium/vitamin D_3 supplementation and that Calceos had unique advantages in terms of taste.

Reginster *et al* did not compare Calceos with other chewable tablets, but rather compared a tablet with similar active ingredients to Calceos with an effervescent tablet. The previous two pages of claims, which had been constructed in a misleading fashion and were largely unsubstantiated by the references cited, would lead the reader to conclude that other calcium/vitamin D_3 supplements should be replaced by Calceos which tasted better and therefore would have better patient adherence rates. The leavepiece in fact contained no data concerning the taste, preference, acceptability or adherence of Calceos either alone or in comparison with either Adcal-D_3 or Calcichew-D_3 Forte. To refer to Adcal-D_3 and Calcichew-D_3 Forte in a leavepiece whose central theme was taste was therefore misleading, in breach of Clause 7.2.

RESPONSE

Galen stated that the page 'Taste the NEW savings with Calceos' was a straightforward price comparison between Calceos and the two market leaders Adcal-D_3 and Calcichew-D_3 Forte. This compared the cost of equivalent dosages of the three agents and was accurate as of the prices in January 2008 when the leavepiece was produced. It made no claims regarding any potential advantages of Calceos over the other two agents beyond that it was the cheapest on the market.

Galen believed that a robust price comparison was not misleading and accordingly not in breach of Clause 7.2.

PANEL RULING

The Panel noted that the leavepiece made a number of claims for taste advantages for Calceos. The context of the cost comparison was an important consideration. The use of the word 'Taste' in the heading to the cost comparison extended this theme and might be read as implying that Calceos had taste advantages over Adcal-D_3 and Calcichew-D_3 Forte. The Panel considered that on balance this implication was misleading and a breach of Clause 7.2 was ruled.

4 Claim 'High adherence with calcium and vitamin D supplements *doubles* the reduction in fracture risk'

This was a heading to a bar chart showing the % reduction of fracture risk for ≥80% adherence (24%), 60-69% adherence (8%) and 50-59% adherence (4%). The bar chart was referenced to a meta-analysis by Tang *et al* (2007). The Calceos logo appeared beneath the bar chart.

COMPLAINT

ProStrakan noted that the Tang *et al* meta-analysis was of 29 trials of calcium, and calcium/vitamin D_3 supplementation. The claim was true. However, the leavepiece contained no data on the adherence of Calceos and it was therefore misleading to associate Calceos with the benefits of high adherence to calcium/vitamin D_3 supplementation. Moreover, in the context of this piece (which misleadingly implied that Calceos had taste and therefore adherence advantages over other products), this claim implied Calceos would deliver greater (perhaps even double) reduction in fracture risk than competitor products. ProStrakan alleged that the claim, in this context, was misleading, in breach of Clause 7.2.

Additionally, none of the eight studies in Tang *et al* that showed high compliance with overall 24% fracture risk reduction used the combination of calcium and vitamin D_3 (1000mg and 800IU) that was the recommended Calceos dose. It was therefore misleading for Galen to make any claim regarding increased fracture risk reduction for Calceos using this reference, in a breach of Clauses 7.2 and 7.4.

Finally, Tang *et al* made clear recommendations about the minimum doses of calcium and vitamin D_3 (1200mg and 800IU respectively) required for best effect. Since Calceos contained only 1000mg of calcium, ProStrakan considered it misleading for Galen to refer to Tang *et al*. A further breach of Clause 7.2 was alleged.

RESPONSE

Galen stated that the purpose of the page was to remind physicians that adherence to calcium and vitamin D_3 supplements was an important factor in the long-term effectiveness of these agents. This was generally accepted and was as applicable to any of the other calcium and vitamin D_3 supplements as it was to Calceos. No claim was made that Calceos would improve adherence, that it had adherence advantages over other products or that it would provide a greater reduction in fracture risk than other products.

Accordingly, Galen believed the statement 'High adherence with calcium and vitamin D_3 supplements doubles the reduction in fracture risk' was not misleading and not in breach of Clause 7.2

Tang *et al* was a large meta-analysis of 29 studies in which 8 studies with compliance of 80% or more reported a significantly greater risk reduction than

those with lower compliance. These 8 studies had widely varying doses of calcium alone (750mg-1600mg) or calcium/vitamin D_3 (500mg calcium/700IU – 1200mg calcium/800IU). If any claim was made, it was that compliance rather than dosage of either calcium alone or calcium and vitamin D_3 was important and in fact the authors reported that they found no relation between compliance and an increased dose of calcium (p=0.57).

No claim was made that Calceos increased fracture risk reduction and Galen believed that the reference supported the statement and was not in breach of Clauses 7.2 or 7.4.

Tang *et al* did indeed make clear recommendations about the minimum doses of calcium alone and separately for vitamin D_3 in combination with calcium. In the discussion the authors stated that:

> 'For calcium only supplementation, a minimum dose of 1200mg is needed for best therapeutic effect. For calcium in combination of vitamin D supplementation, a minimum dose of 800IU of vitamin D is recommended' and
>
> 'On the basis of our recommended minimum dose of 1200mg of calcium or 800IU of vitamin D….'

The authors made recommendations for calcium alone and for vitamin D_3 in combination with calcium but not for a combined calcium and vitamin D_3 preparation. As Calceos contained 800IU vitamin D_3 in combination with calcium it complied with the recommendations in the paper and was not a breach of Clause 7.2 either in the leavepiece or the letter to the hospital consultant.

PANEL RULING

The Panel noted that the statement at issue, referenced to Tang *et al*, claimed that high adherence with calcium and vitamin D_3 supplements would double the reduction in fracture risk. It also included the Calceos logo and appeared immediately on turning the front page which claimed 'Calceos is formulated with Taste in mind' and opposite page 2 which read 'Taste is important for: … Long-term patient adherence with calcium/vitamin D chewable tablets'. The claim would be read as applying to Calceos ie that high adherence with Calceos had been shown to double the reduction in fracture risk. This was not so.

None of the studies in Tang *et al* meta-analysis used the Calceos dose (ie a fixed combination of calcium 1000mg and vitamin D_3 800IU). Thus the Panel considered that in the context in which they appeared the bar chart from Tang *et al* and the claim were misleading; the claim had not been substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

B Letter to a hospital consultant

COMPLAINT

ProStrakan stated that this letter, signed by an employee of Galen, contained information regarding Calceos. The letter referenced the Tang *et al* review of calcium/vitamin D_3 supplementation. As discussed above, ProStrakan believed this was misleading, in breach of Clause 7.2, as Tang *et al* recommended a dose of calcium that was higher than that contained in Calceos.

RESPONSE

Galen submitted that this allegation was covered in point A5 above.

PANEL RULING

The Panel noted that the letter to the consultant provided by Galen did not refer to any published studies. The Business Case document which accompanied the letter did refer to Tang *et al* but the document did not appear to be the subject of ProStrakan's complaint. There was no reference in the letter to Tang *et al* and no mention of adherence and fracture risk. The Panel ruled no breach of Clause 7.2 with regard to the allegations made about the letter to the consultant.

Complaint received **18 August 2008**

Case completed **5 November 2008**