CASE AUTH/2019/7/07

LEO PHARMA v GALDERMA

Silkis 'Dear Doctor' letter

Leo Pharma complained about a Silkis Ointment (calcitriol) letter sent to GPs by Galderma following Leo's announcement of the impending discontinuation of Dovonex Ointment (calcipotriol). The letter suggested that for psoriasis patients who preferred a topical Vitamin D medicine, then Silkis might be a suitable alternative.

Leo alleged that the claim 'Silkis has demonstrated comparable efficacy to a steroid in mild to moderate psoriasis' which was referenced to Camarasa *et al* (2003) exaggerated the efficacy of Silkis compared to a steroid and implied that Silkis was similar or equivalent in efficacy to a steroid in mild to moderate psoriasis.

The Panel noted that Camarasa *et al* had compared the efficacy and duration of remission post-treatment of Silkis ointment with betamethasone dipropionate ointment in patients with chronic plaque-type psoriasis of at least moderate severity. The authors described the efficacy of the two medicines as broadly comparable; there were, however, some differences between them. Global improvement and global severity scored at treatment endpoint showed statistically significant differences in favour of betamethasone dipropionate ($p<0.05$); however the absolute reduction in psoriasis area and severity index (PASI) was comparable between the groups. A statistically significantly ($p<0.01$) higher proportion of responders remained in remission following Silkis treatment (48%) than betamethasone treatment (25%).

The Panel considered that, given the findings of Camarasa *et al*, the claim 'Silkis has demonstrated comparable efficacy to a steroid in mild to moderate psoriasis' was too broad such that it was misleading. It implied that in patients with mild to moderate psoriasis, the efficacy observed with Silkis had been shown to be statistically similar to that of a steroid which was not so. The Panel considered that the claim was misleading in this regard and could not be substantiated. Breaches of the Code were ruled.

Leo alleged that the claim 'Silkis ointment has demonstrated greater cosmetic acceptability when compared with Dovonex ointment' referenced to Marty *et al* (2005) relied on conflicting evidence and in that regard was inaccurate and misleading and could not be substantiated.

The Panel noted that Marty *et al* compared the viscosity and clinical acceptability of, *inter alia*, Silkis Ointment and Dovonex Ointment when applied to psoriatic skin. Compared to Dovonex, Silkis Ointment was statistically significantly superior in terms of fluidity and spreadability. There was no difference between the products in terms of sticky skin sensation. No statistically significant difference was shown between Silkis and Dovonex for pleasant consistency, pleasant sensation on the skin, nourishing properties and pleasant use. Regarding the overall subject preference there was no difference in preference between Silkis and Dovonex.

The Panel considered that the claim 'Silkis ointment has demonstrated greater cosmetic acceptability when compared with Dovonex ointment' was too broad given the data in Marty *et al*. Cosmetic acceptability covered a number of aspects and in most there had been no statistically significant difference between Silkis and Dovonex. The areas where Silkis had been shown to be superior to Dovonex were limited to fluidity and spreadability. The Panel considered that the claim was misleading as alleged and could not be substantiated. Breaches of the Code were ruled.

Leo alleged that the claim '…Silkis can provide a cost effective option within the Vitamin D topical market…' was inaccurate and misleading because although Silkis might cost less than competitors, it was not necessarily cost effective. The only potential substantiation that had been provided was that the cost of a 100g tube of Silkis was £16.34. This was a price not a cost-effectiveness assessment. Galderma had not, to Leo's knowledge, performed any health economic evaluation to support this claim. Galderma had undertaken to be more explicit in future promotional material by referring to the comparative costs (per gram) of the two products but this still did not justify the continued use of the term 'cost effective' in its material. Leo was concerned that Galderma did not appreciate the meaning of the term 'cost effective' and had confused 'cheap' with 'cost effective'.

Furthermore, Leo believed that Galderma was disingenuous when it maintained that Silkis might be cost effective merely by including the letter 'a' in its claim. If this was acceptable by implication, any medicine that had any effect, no matter how small, and any cost, no matter how big might be described as being cost effective.

The Panel considered that there was an element of comparison involved with a claim 'a cost effective option', even if no other product was mentioned. The claim at issue referred to the vitamin D topical market. Although Dovonex Ointment was to be discontinued Curatoderm Ointment would still be available. The claim for cost-effectiveness had been related solely to the acquisition cost of Silkis. The letter had not dealt with the economic evaluation of the effectiveness of Silkis and no data had been

provided to substantiate the claim. In the Panel's view the term 'cost effective' referred to more than just the acquisition cost of a medicine. Other factors such as relative efficacy, incidence of side effects, etc, had to be taken into account. The Panel decided that the claim 'Cost effective' was misleading and had not been substantiated and ruled breaches of the Code.

Leo Pharma complained about a 'Dear Doctor' promotional letter for Silkis Ointment (calcitriol) (ref CAL/11/0307) sent to GPs by Galderma (UK) Limited. The letter was sent following Leo's announcement of the impending discontinuation of Dovonex Ointment (calcipotriol) and suggested that for psoriasis patients who preferred a topical Vitamin D medicine, then Silkis might be a suitable alternative.

1 Claim 'Silkis has demonstrated comparable efficacy to a steroid in mild to moderate psoriasis'

This claim was referenced to Camarasa *et al* (2003).

COMPLAINT

Leo alleged that the claim exaggerated the efficacy of Silkis compared to a steroid and in that regard was inaccurate and misleading in breach of Clause 7.2 of the Code. Leo further alleged that the claim could not be substantiated in breach of Clause 7.4.

Leo submitted that the dictionary definition of 'comparable' provided two potential meanings, either 'worthy of comparison' or 'similar or equivalent'. In the context of this claim it was self-evident that the intended meaning and the meaning which all readers would infer was 'similar or equivalent'. In effect Galderma had claimed that Silkis was similar or equivalent in efficacy to a steroid in mild to moderate psoriasis.

Camarasa *et al* stated that both treatments were efficacious but that 'Global improvement and global severity scores at treatment endpoint showed statistically significant differences in favour of betamethasone dipropionate ($p<0.05$)'. In the efficacy evaluation section it was stated that 'It was noted that the proportion of patients whose psoriasis completely cleared was twice as large with betamethasone dipropionate ointment (20%) in comparison with those who cleared with Silkis ointment (9%)'. Bearing in mind that this study was supported by a grant from Galderma and hence any potential bias in describing the results was likely to lean in favour of Galderma's product, the strongest claim that the authors made in their discussion was that the active treatments were 'broadly comparable in terms of efficacy', the word 'broadly' markedly diminished the degree of similarity being described and so Leo believed that Galderma had overstated and exaggerated the findings in its claim that the efficacy of Silkis was 'comparable' to a steroid.

A literature search had revealed no alternative papers capable of substantiating this claim.

RESPONSE

Galderma submitted that the claim was for comparable efficacy, not identical or superior efficacy, which could not be substantiated. The primary efficacy variable of Camarasa *et al* was to show a difference between the treatments of at least 0.6 in global improvement score at endpoint – this was the basis of the sample size calculation. The results showed that Silkis decreased the global score by a mean of 1.58 compared with 1.36 for betamethasone. This meant that there was no significant difference between the two ointments. The authors chose a difference of 0.6 as being clinically relevant. Thus, the ointments were comparable in both statistical and clinical terms.

The following statements should be noted regarding comparable efficacy made in Camarasa *et al*:

- 'Both calcitriol 3μg/g ointment and betamethasone dipropionate 0.05% ointment were found to be efficacious. Similar proportions of patients (79% in the calcitriol group and 82% in the betamethasone group) showed definite or considerable improvement in their psoriasis, or total clearance of lesions by treatment endpoint (Table II)'.
- 'Both treatment groups showed a clinically relevant decrease in the mean global severity score which, at endpoint, was 1.58 for the calcitriol group and 1.36 for the betamethasone group ($p>0.05$). Each treatment also resulted in a marked improvement in the PASI [psoriasis area and severity index] from baseline to endpoint (Table II), with the absolute reduction in the mean PASI at endpoint being comparable between groups ($p>0.05$)'.

The authors concluded that either treatment could be used to give a good clinical response. Thus the claim accurately reflected the conclusions of Camarasa *et al*, which substantiated the claim. Galderma thus denied a breach of Clauses 7.2 and 7.4.

Galderma noted that all of the authors were leading independent clinicians and that the study was published in a respected peer-reviewed publication. Galderma questioned whether Leo, in its comments about sponsorship and authorship of Camarasa *et al*, had challenged the professional conduct of the investigators or the independence of the publication. This was particularly relevant given that at least two of the authors, Ortonne and Dubertret, had previously published several papers supporting Leo's topical vitamin D products. Indeed publications authored by these individuals were cited within Leo promotional materials.

PANEL RULING

The Panel considered that, in common parlance, if two medicines were described as comparable then prescribers and patients would generally not mind which one was used. The Code required material including comparisons to have a statistical foundation. Clinical relevance was an important consideration.

The Panel noted that Camarasa *et al* had compared the efficacy and duration of remission post-treatment of Silkis ointment with betamethasone dipropionate ointment in patients with chronic plaque-type psoriasis of at least moderate severity. The authors described the efficacy of the two medicines as broadly comparable; there were, however, some differences between them. Global improvement and global severity scored at treatment endpoint showed statistically significant differences in favour of betamethasone dipropionate ($p<0.05$); however the absolute reduction in psoriasis area and severity index (PASI) was comparable between the groups. A statistically significantly ($p<0.01$) higher proportion of responders remained in remission following Silkis treatment (48%) than betamethasone treatment (25%).

The Panel considered that, given the findings of Camarasa *et al*, the claim 'Silkis has demonstrated comparable efficacy to a steroid in mild to moderate psoriasis' was too broad such that it was misleading. It implied that in patients with mild to moderate psoriasis, the efficacy observed with Silkis had been shown to be statistically similar to that of a steroid which was not so. The Panel considered that the claim was misleading in this regard and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

2 Claim 'Silkis ointment has demonstrated greater cosmetic acceptability when compared with Dovonex ointment'

This claim was referenced to Marty *et al* (2005).

COMPLAINT

Leo alleged that the claim relied on conflicting evidence and in that regard was inaccurate and misleading in breach of Clause 7.2. Leo further alleged that the claim could not be substantiated in breach of Clause 7.4.

Leo noted that Marty *et al* suggested that Silkis was better than Dovonex in only 2 out of 7 variables, namely fluidity and spreadability, however, calcipotriol was superior in the sticky skin sensation characteristic. The authors noted that 'no statistical difference between calcitriol and its competitors was noted for: pleasant consistency, pleasant sensation on the skin, nourishing properties and pleasant use'. The claim at issue was for overall cosmetic acceptability rather than individual variables tested and in this respect, Marty *et al* stated 'there was no statistically significant difference in the aspect between Silkis and Dovonex'. Furthermore, regarding overall subject preference it was stated that 'there was no difference in preference between Silkis and Dovonex'.

Despite these fairly definitive statements Marty *et al* was then rather unclear as to how it arrived at the final statement in its discussion and conclusion that 'significant differences in the subjects' cosmetic acceptability in favour of calcitriol 3μg/g ointment compared to calcipotriol 50μg/g and tacalcitol 4μg/g ointments could be demonstrated'. Indeed, the introductory abstract stated that calcitriol and calcipotriol showed similar results to each other compared to tacalcitol whose viscoelastic parameters were 4 times higher. The authors did not provide any information on sponsorship.

Given the apparently conflicting statements and the uncertainty of the true results and conclusions to be gleaned from Marty *et al*, it would be unwise and potentially misleading to rely on this one paper in isolation to substantiate any claim of superiority in cosmetic acceptability between calcitriol and calcipotriol. No additional substantiation in support of this claim could be found.

RESPONSE

Galderma noted that Marty *et al* assessed the *in vitro* rheological properties of three vitamin D ointments and paralleled those results with an assessment of the clinical acceptability of the three ointments when applied to the skin of psoriatic subjects.

The *in vitro* rheological assessments showed that Silkis Ointment had better fluidity and flow than Dovonex which suggested that it was easier to apply to the skin.

The clinical acceptability assessment investigated primarily patients' views on fluidity, ease of spread and sticky skin sensation by questionnaire. Questions were also asked on the aspect, consistency, sensation on the skin, nourishment of the skin and the use.

The results showed that in two of the three primary assessment parameters (fluidity and ease of spread) Silkis was significantly superior to Dovonex. There was no significant difference between the two products on the third parameter, the sensation of stickiness. The supplementary questions did not reveal any further differences between the products. The authors stated that Silkis had optimal rheological characteristics for topical application to psoriatic skin and these *in vitro* results were confirmed by assessment of patient perception.

Marty *et al* concluded that 'Significant differences in the subjects' cosmetic acceptability in favour of calcitriol 3μg/g ointment compared to calcipotriol 50μg/g and tacalcitol 4μg/g ointment could be demonstrated'.

This study provided clear objective data to support the claim that Silkis had demonstrated greater cosmetic acceptability when compared to Dovonex Ointment.

Galderma denied a breach of Clauses 7.2 and 7.4.

PANEL RULING

The Panel noted that Marty *et al* compared the viscosity and clinical acceptability of, *inter alia*, Silkis Ointment and Dovonex Ointment when applied to psoriatic skin. Patients with mild to moderate psoriasis were asked to compare Silkis with Dovonex over a two day period. After each product application patients were asked about the fluidity, easiness to spread and

sticky skin. Further questions concerned the aspect [sic], consistency, sensation on the skin, nourishment of the skin and the use of each product. Compared to Dovonex, Silkis Ointment was statistically significantly superior in terms of fluidity and spreadability. There was no difference between the products in terms of sticky skin sensation. No statistically significant difference was shown between Silkis and Dovonex for pleasant consistency, pleasant sensation on the skin, nourishing properties and pleasant use. Regarding the overall subject preference there was no difference in preference between Silkis and Dovonex.

The Panel considered that the claim 'Silkis ointment has demonstrated greater cosmetic acceptability when compared with Dovonex ointment' was too broad given the data in Marty *et al*. Cosmetic acceptability covered a number of aspects and in most there had been no statistically significant difference between Silkis and Dovonex. The areas where Silkis had been shown to be superior to Dovonex were limited to fluidity and spreadability. The Panel considered that the claim was misleading as alleged and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

3 Claim '…Silkis can provide a cost effective option within the Vitamin D topical market…'

COMPLAINT

Leo alleged that the claim was inaccurate and misleading because although Silkis might cost less than competitors, it was not necessarily cost effective and so breached Clause 7.2. It also breached Clause 7.4 because it was incapable of substantiation and Clause 7.5 because on request, Galderma had failed to provide any substantiation of the claim.

The only potential substantiation that had been provided was that the cost of a 100g tube of Silkis was £16.34. This was a price not a cost-effectiveness assessment. Galderma had not, to Leo's knowledge, performed any health economic evaluation to support this claim. Galderma had undertaken to be more explicit in future promotional material by referring to the comparative costs (per gram) of the two products but this still did not justify the continued use of the term 'cost effective' in its material. Leo was concerned that Galderma did not appreciate the meaning of the term 'cost effective' and had confused 'cheap' with 'cost effective'.

Furthermore, Leo believed that Galderma was disingenuous when it maintained that Silkis might be cost effective merely by including the letter 'a' in its claim. If this was acceptable by implication, any medicine that had any effect, no matter how small, and any cost, no matter how big might be described as being cost effective. Leo believed it was inaccurate, misleading and unacceptable to make a claim of cost effectiveness for any product without reference to a comparative health economic evaluation of some sort that was relevant to the market in question.

RESPONSE

Galderma noted that the claim did not mean that Silkis had been shown to be more cost effective than any other medicine. This would indeed have been an irrelevant comparison, given that Leo was writing to health professionals announcing the imminent withdrawal of its vitamin D ointment from the UK market. Galderma used the word 'a' which clearly showed that it was aware that many factors had to be taken into account when assessing the economic worth of a medicine. Galderma could not see, from the Code, that a health economic evaluation was a prerequisite for a claim of a product being 'a cost-effective option'. Galderma accepted that if it claimed that Silkis was either the only cost effective choice or a more cost effective choice than a named therapy then data would have been needed to back this up.

Galderma denied breaches of Clauses 7.2, 7.4 and 7.5.

PANEL RULING

The Panel noted that the supplementary information to Clause 7.2 of the Code stated that care must be taken that any claim involving the economic evaluation of a medicine was borne out by the data and did not exaggerate its significance. The Panel considered that there was an element of comparison involved with the claim 'a cost effective option', even if no other product was mentioned. The claim at issue referred to the vitamin D topical market. Although Dovonex Ointment was to be discontinued Curatoderm Ointment would still be available. The claim for cost-effectiveness had been related solely to the acquisition cost of Silkis. The letter had not dealt with the economic evaluation of the effectiveness of Silkis and no data had been provided to substantiate the claim. In the Panel's view the term 'cost effective' referred to more than just the acquisition cost of a medicine. Other factors such as relative efficacy, incidence of side effects, etc, had to be taken into account. The Panel decided that the claim 'Cost effective' was misleading and had not been substantiated and ruled breaches of Clauses 7.2, 7.4 and 7.5.

Complaint received	**11 July 2007**
Case completed	**5 September 2007**