CASE AUTH/3501/4/21

COMPLAINANT v LEO

Protopic web page and an alleged breach of undertaking

An anonymous, contactable complainant alleged that a number of claims about Protopic (tacrolimus) on the 'At a glance' section of the uk.dermaworld.eu website were inaccurate and erroneous. Protopic, was a non-steroid ointment available as 0.1% (for adults and adolescents aged 16 years and over) and 0.03% (for adults, adolescents and children aged 2 years and over) and was indicated for either flare treatment or maintenance treatment in moderate to severe atopic dermatitis in patients who were not responsive to or were intolerant of topical corticosteroids.

The detailed response from Leo is given below.

1 Image used on the webpage

The complainant stated that the image on the webpage was no different to the principle of the image which was ruled in breach of the Code in Case AUTH/2418/7/11. The complainant alleged that as the Protopic summary of product characteristics (SPC) contained a warning around exposure to the sun, it was not appropriate to show a patient who was tanned and in short sleeves. There was no wording at all on the page about the risks of UV exposure. The complainant alleged that the image did not promote Protopic in accordance with the requirements of its SPC and that it breached the undertaking given in Case AUTH/2418/7/11.

The Panel noted the image in question featured, on the left-hand side, a man wearing a long-sleeved shirt and trousers, who appeared to be walking in circles in the rain, holding an open umbrella; the left-hand side of the image appeared to be in dark, stormy conditions. The right-hand side of the image depicted the same man walking out of the rain and into brighter weather, with blue skies and his umbrella closed, and now wearing a short-sleeved shirt and trousers. The man was thus wearing less clothing and consequently exposing more skin than in the left-hand side of the image. The image was overlaid with the Protopic product logo and the claim 'Protopic Moving beyond topical corticosteroids in moderate to severe atopic dermatitis'.

The Panel noted that Section 4.4 (Special warnings and precautions for use) of the Protopic SPCs stated, *inter alia*:

> **'Exposure of the skin to sunlight should be minimised and the use of ultraviolet (UV) light from a solarium, therapy with UVB or UVA in combination with psoralens (PUVA) should be avoided during use of Protopic ointment (see section 5.3). Physicians should advise patients on appropriate sun protection methods, such as minimisation of the time in the sun, use of a sunscreen product and covering of the**

skin with appropriate clothing. Protopic ointment should not be applied to lesions that are considered to be potentially malignant or pre-malignant.'

The Protopic patient information leaflet stated:

> **'If you spend time outdoors after applying Protopic, use a sunscreen and wear loose fitting clothing that protects the skin from the sun. In addition, ask your doctor for advice on other appropriate sun protection methods'.**

Whilst the Panel acknowledged that patients treated with Protopic would not entirely avoid being outdoors, it was concerned that there was a clear contrast in the images before and after treatment which showed a man who had changed from a long sleeve to a short sleeve top and had closed his umbrella when walking into better and brighter weather conditions; the Panel considered that this implied that the patient did not have to be concerned about exposure to sunlight whilst on treatment and that was not so. The Panel considered that this was inconsistent with the particulars listed in the Protopic SPC and high standards had not been maintained. Breaches of the Code were ruled.

The image on the right did not show the model as 'demonstrably tanned compared to the picture of him on the left-hand side' as alleged and therefore the Panel did not consider that the image was misleading on the narrow point alleged; no breach of the Code was ruled.

The Panel noted in Case AUTH/2418/7/11, Astellas was ruled in breach of the Code as the front cover of a Protopic leavepiece, which depicted a woman wearing less clothing and consequently exposing more skin than those around her, implied that the patient did not have to be concerned about exposure to sun which was not so and was inconsistent with the particulars listed in the Protopic SPC, which was upheld on appeal. Astellas' undertaking was signed in 2011 which was prior to Protopic being divested to Leo Pharma in 2018.

The Panel considered that Leo, following the divestment, in addition to its general responsibility for complying with the Code might have a responsibility to ensure that similar breaches of the Code in relation to Protopic were avoided. Whilst the Panel considered that the matter was sufficiently similar to that which had been ruled in breach in Case AUTH/2418/7/11, on balance, the Panel decided that the requirement in the Code applied to the company concerned and thus ruled no breaches of the Code including Clause 2 as that undertaking was given by Astellas and not Leo. The Panel considered, however, that the similar nature of the breaches meant that high standards had not been maintained and thus ruled a breach of the Code in that regard.

2 'Protopic Moving beyond topical corticosteroids in moderate to severe atopic dermatitis'

The complainant alleged that the statement was misleading and the promotion was inconsistent with the SPC as the phrase 'moving beyond' implied that Protopic was more efficacious or advanced than topical corticosteroids, yet the SPC did not support that claim. The claim had not been referenced so the information was not sufficiently complete to enable the reader to assess its credibility.

The Panel considered that the expression 'moving beyond' was ambiguous. However, the claim did not imply that Protopic was more efficacious or advanced compared to topical corticosteroids as alleged. The complainant had not discharged his/her burden of proof that the claim was inconsistent with the SPC, misleading or incapable of substantiation as alleged and thus based on the narrow allegation the Panel ruled no breaches of the Code.

The Panel considered that the complainant had not discharged his/her burden of proof that the statement needed to be referenced to a published study, nor that Leo had failed to maintain high standards. No breaches of the Code were ruled including Clause 2.

3 'Protopic is designed for moderate to severe [atopic dermatitis]'

The complainant alleged that the claim was inconsistent with the SPC which stated that Protopic could be used for flare treatment in adults and adolescents in the treatment of moderate to severe atopic dermatitis who were not adequately responsive to or intolerant of conventional therapies such as topical corticosteroids. Therefore, Protopic should not be promoted or used as a first-line agent in moderate to severe atopic dermatitis as suggested and was only suitable for a particular population at a certain dosage for a particular length of time. The complainant alleged that this broad claim was misleading and prejudiced patient safety.

The Panel noted that the Protopic indication was not stated on the 'at a glance' webpage at issue but the indication for flare treatment was stated on the preceding webpage which provided the link to the 'at a glance' webpage.

It appeared to the Panel that health professionals would likely access the 'at a glance' webpage from the 'treatments' page, which included Protopic's indication, and therefore would not be misled that the claim at issue incorrectly implied that Protopic could be used as a first-line agent as alleged. Although it would have been helpful if the full indication for Protopic was stated on the 'at a glance' webpage, the Panel considered that the complainant had not established that the claim 'Protopic is designed for moderate to severe AD [atopic dermatitis]' in the context of the webpage and website was inconsistent with the SPC or misleading as alleged. The Panel ruled no breaches of the Code including Clause 2.

4 'Protopic targets inflammation + Protopic supports repair of skin barrier'

The complainant stated that for the claim that Protopic targeted inflammation, the data in the SPC was limited to *in vitro* human cells and animal models and could not be extrapolated to the clinical setting. The claim was not consistent with the SPC.

The complainant alleged that the SPC wording did not support that Protopic targeted inflammation in a clinical setting, was misleading and not capable of substantiation.

For the second half of the claim, the complainant stated that the reference, Xhauflaire-Uhodae *et al* (2007) was not powered to support such a claim nor did it conclude that

Protopic supported skin barrier repair. The complainant alleged that the claim was unfair, misleading and not capable of substantiation.

The claim 'Protopic targets inflammation' was referenced to the Protopic SPC. The Panel noted Leo's submission that as per the SPC, the efficacy and safety of Protopic was assessed in more than 18,500 patients treated with tacrolimus ointment in Phase I to Phase III clinical trials and that several of those trials included as a primary end-point, response rate defined as the proportion of patients with at least 60% improvement in the modified Eczema Area and Severity Index between baseline and a specified time point. The Panel further noted Leo's submission that based on the modified Eczema Area and Severity Index 60 response rate, which included a measure of inflammation, Protopic had demonstrated clinical evidence as to its effect on inflammation.

The Panel considered that the complainant had not discharged his/her burden of proof that the claim 'Protopic targets inflammation' was inconsistent with the SPC, misleading or incapable of substantiation as alleged and the Panel therefore ruled no breaches of the Code.

The claim 'Protopic supports repair of skin barrier' was referenced to Xhauflaire-UhodaE *et al*, a double-blind randomised study which compared tacrolimus and betamethasone valerate and stated that during treatment, both compounds yielded a similar improvement in skin barrier function. The Panel further noted that Danby *et al* (2014) compared the effects of betamethasone valerate 0.1% cream and tacrolimus 0.1% ointment and concluded that tacrolimus 0.1% ointment improved the condition of the skin barrier.

The Panel noted that the claim was not comparing Protopic to any other treatment. On the evidence before it, the complainant had not discharged his/her burden of proof that the claim 'Protopic supports repair of skin barrier' was misleading or incapable of substantiation as alleged and the Panel therefore ruled no breaches of the Code including Clause 2.

5 'Help patients know what to expect when they start treatment with Protopic' and patient 'before and after' photographs

The complainant alleged that the statement implied that the page should be used by a health professional in a patient consultation as a visual aid and should therefore have contained the mandatory wording for patients using a medicine as per the Code. Such information for use with patients should not be a part of a promotional webpage which in turn promoted the product to the public.

The images were labelled as being taken at baseline and 'After 4 weeks' but there was no information as to whether the patient was treated with Protopic for an initial flare or for maintenance therapy as the posology varied accordingly. The complainant alleged that the information was ambiguous and incomplete.

For flare treatment, the SPC recommended that if no signs of improvement were seen after two weeks of treatment, further treatment options should be considered. The complainant alleged that the inclusion of a baseline and 4 week image suggested that

Protopic should be used for 4 weeks and then assessed, which was misleading. The incomplete and selective information prejudiced patient safety and the images did not promote the rational use of a medicine as patients might be left on Protopic unnecessarily and for longer than appropriate.

In the Panel's view, the photographs were for health professionals to understand what to expect following treatment so that they could explain this to their patients. Consequently, the Panel did not consider that the images promoted a prescription only medicine to the public or were for viewing by the public and therefore no breaches of the Code were ruled including Clause 2.

The Panel did not consider that the complainant had established that photographs depicting results after 4 weeks of treatment, in the material at issue, meant that Protopic had been promoted in a manner inconsistent with its SPC as alleged. Nor did the Panel consider that the photographs were misleading or did not promote the rational use of the medicine as alleged. No breaches of the Code were ruled including Clause 2.

6 Lack of warning regarding sun protection methods

The complainant noted that under the heading 'Preparing your patients for their Protopic 0.1% treatment' was a mention of skin irritation, burning sensation and pruritis to the left of an outline sketch of a woman in a short sleeveless dress with exposed arms, legs and neck; but there was no wording to reflect the warning from Section 4.4 of the SPC. The complainant alleged that the image together with the lack of information on precautions around UV exposure did not give an accurate presentation of Protopic; it prejudiced patient safety and was misleading.

The Panel noted that the website contained a link to the prescribing information; it did not have a copy and Leo had made no submission in that regard. Whether a special warning or precaution also needed to be highlighted in another section of the promotional material depended on a consideration of all of the circumstances including the nature of the warning/precaution and the content, layout, audience and intended use of the material.

The Panel noted that next to the sketch of a lady in a short sleeveless dress and beneath the heading 'Preparing your patients for their Protopic 0.1% treatment', it stated:

> **'1 in 2 patients experienced some type of skin irritation at the site of application.**
>
> **Burning sensation and pruritus were very common and tended to resolve within one week of starting treatment.'**

The Panel noted that the sketch was very basic and considered that it was difficult to tell if the individual was indoors or outdoors. In the Panel's view, this section of the material appeared to focus on application site reactions. The Panel did not consider that the sketch implied that there were no concerns with sun exposure. Whilst it might have been helpful within this section of the material to include the special warning and precaution for use regarding minimising exposure of the skin to sunlight etc, the Panel did not

consider that the complainant had established that its omission rendered the material misleading as alleged. The Panel ruled no breaches of the Code including Clause 2.

7 'Protopic 0.1% delays time to next flare when used proactively' and associated graph

The complainant stated that the study design and primary endpoint in the study had not been included to put the claim in context as the results were in a sub-population.

The complainant alleged that the claim and graph around delaying time to the next flare was misleading as it did not take into consideration the time taken to undergo 'reactive' management (6 weeks in this study) and before 'proactive' management could start.

The complainant alleged that although the graph stated that it had been adapted from the Protopic SPC, it exaggerated the efficacy of Protopic, was misleading, incompatible with the SPC and not capable of substantiation. The artwork itself was misleading as it showed only one flare for Protopic over 1 year when more than one flare would be expected.

The Panel noted that Section 4.1 of the Protopic 0.1% ointment SPC stated that it was indicated in adults and adolescents (16 years of age and above) for:

> **<u>Flare treatment</u>**
> **Treatment of moderate to severe atopic dermatitis in adults who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids.**
>
> **<u>Maintenance treatment</u>**
> **Treatment of moderate to severe atopic dermatitis for the prevention of flares and the prolongation of flare-free intervals in patients experiencing a high frequency of disease exacerbations (ie occurring 4 or more times per year) who have had an initial response to a maximum of 6 weeks treatment of twice daily tacrolimus ointment (lesions cleared, almost cleared or mildly affected).**

The Panel noted the lack of information about the study design on the webpage in question; the webpage made no reference to the fact that patients in this study had had previous treatment with tacrolimus twice daily until clear, almost clear or mild disease for a maximum of 6 weeks before being randomised to receive either tacrolimus or vehicle, once a day twice weekly. The misleading impression given was compounded by the fact that the indication for Protopic 0.1% as a maintenance treatment had not been stated on the webpage in question or the preceding webpage and therefore it was not clear to health professionals reading the material that Protopic was only to be used as a maintenance therapy in patients who had had an initial response to a maximum of 6 weeks treatment of twice daily tacrolimus ointment (lesions cleared, almost cleared or mildly affected). Furthermore, the webpage did not make clear the dosing frequency (once a day twice weekly) for which the results presented were based upon. The Panel considered that the webpage had insufficient information about the study design to put the claim 'Protopic 0.1% delays time to next flare when used proactively' into context and a breach of the Code was ruled.

The Panel noted that the graph in the material in question stated that the median time to first disease exacerbation was 15 days for vehicle and 142 days for Protopic 0.1% when in fact the SPC stated that it was 14 days vs 123 days, respectively. Leo submitted that this was an error. The error in the graph misleadingly implied that Protopic 0.1% delayed time to disease exacerbation for a longer period than the study had reported. Further the graph was inconsistent with the study data in section 5.1 of the SPC and was incapable of substantiation; breaches of the Code were ruled. High standards had not been maintained and a further breach of the Code was ruled.

The Panel considered that the graph implied that patients taking Protopic 0.1% in the study had a median of 1 flare during the 12 month study period vs 6.8 flares for those patients taking the vehicle; the SPC stated that the median number of disease exacerbations adjusted for time at risk was 1.0 for tacrolimus 0.1% vs 6.8 for vehicle. The Panel considered that the complainant had not established that the data regarding number of flares in the graph was misleading as alleged and no breach of the Code was ruled.

The Panel noted its rulings of breaches of the Code above which it considered covered the matter and no breach of Clause 2 was ruled.

8 Use of 0.1% Protopic

The complainant alleged that Leo only presented information on the higher strength of tacrolimus and its claims and clinical images would suggest it was encouraging long-term use of the product, ie proactive management of flares. There was no information to reflect the SPC recommendation to use the lowest strength and frequency for the shortest duration necessary, as determined by the physician's evaluation of the clinical condition; it was likely to prejudice patient safety.

The Panel considered that the complainant had not established that the material encouraged use of Protopic 0.1% long term. Reference to its use proactively did not, in the Panel's view, imply that the medicine should be used indefinitely. The SPC and material stated that Protopic treatment should be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis. In the Panel's view, whilst it would have been helpful to have stated on the webpage the information from the SPC that in relation to maintenance treatment, after 12 months, a review of the patient should be conducted by the physician and a decision taken whether to continue maintenance treatment in the absence of safety data beyond 12 months, the Panel did not consider that the omission of this information on the webpage misleadingly implied that Protopic 0.1% should be used long-term as alleged or that promotion was inconsistent with the particulars in the SPC. No breaches of the Code were ruled including no breach of Clause 2.

9 Date of the SPC used as a reference

The complainant noted that the web page in question used the Protopic SPC as a reference without a date of last revision. The date of the page was May 2019 and the SPC

for Protopic was updated in August 2020. The complainant stated that it appeared that the content of the web page was not reviewed after that update and the reference used was not clear.

The Panel noted Leo's submission that the changes made to the SPC in August 2020 had no bearing on the existing content of the material in question apart from the prescribing information which had been amended and separately certified in September 2020. The Panel did not have a copy of this prescribing information.

The Panel did not consider that the complainant had established that reference to the Protopic SPC on the webpage, without providing the SPC date of revision, in itself, was misleading as alleged nor failed to maintain high standards and no breaches of the Code was ruled including Clause 2 on this narrow point.

Overall

The Panel considered that its rulings adequately covered each matter and that further rulings in relation to the overall case were not warranted in relation to the requirement to maintain high standards and Clause 2; no further breaches were ruled in that regard.

An anonymous, contactable complainant alleged that a number of claims about Protopic (tacrolimus) on the 'At a glance' section (ref MAT-21383) of the uk.dermaworld.eu website were inaccurate and erroneous. The website, created by Leo Pharma in the UK and Ireland, was intended for UK and Ireland health professionals. Protopic, was a non-steroid ointment available as 0.1% (for adults and adolescents aged 16 years and over) and 0.03% (for adults, adolescents and children aged 2 years and over) and was indicated for either flare treatment or maintenance treatment in moderate to severe atopic dermatitis in patients who were not responsive to or were intolerant of topical corticosteroids.

By way of background, Leo stated that patient safety was paramount to the company and it took its obligations and commitment to the letter and spirit of the Code extremely seriously. The focus of the 'At a glance' web page was to provide a top-line, condensed introduction to the Protopic range of products, aimed at health professionals. Before accessing the information, readers were presented with the product's indication for the treatment of flares on the 'Treatments' page (a PDF of the web page and a link to it was provided) which stated:

> 'Protopic is a non-steroid ointment recommended for the treatment of moderate to severe atopic dermatitis (AD) in patients who are not responsive to or are intolerant of topical corticosteroids (TCS). It comes in two strengths:
> • 0.1%: For adults and adolescents ≥ 16 years
> • 0.03%: For adults, adolescents and children ≥ 2 years'

Leo submitted that clicking 'At a glance' took the health professional to a webpage entitled 'Moving beyond topical corticosteroids in moderate to severe atopic dermatitis'; the intention of that webpage was designed to raise awareness of treating patients in whom previous agents (topical corticosteroids) had not resulted in an adequate response, or in whom they were intolerant of, as illustrated by the patient walking around in circles before progressing to the next tier of or alternative treatment.

1 Image used on the webpage

COMPLAINT

The complainant stated that the image on the webpage was no different to the principle of the image which was ruled in breach of the Code in Case AUTH/2418/7/11 for Protopic. This time there was a man walking in a circle in a long-sleeved shirt. On the right-hand side of the picture, he was wearing a short-sleeved polo shirt and was demonstrably tanned compared to the picture of him on the left-hand side of the picture. It was clear that there was sun in the image on the right as the sunlight was reflected on the man's face, neck and arms. The complainant alleged that as the Protopic summary of product characteristics (SPC) contained a warning around exposure to the sun, it was not appropriate to show a patient who was tanned and in short sleeves. There was no wording at all on the page about the risks of UV exposure. The complainant alleged that the image did not promote Protopic in accordance with the requirements of its SPC because UV exposure should be avoided when it was used as per Section 4.4 of the SPC.

The omission of this minimised the safety issue and avoided mentioning the effort that patients must make with regard to sun exposure when it came to using Protopic. The complainant alleged that the image represented a breach of undertaking from Case AUTH/2418/7/11.

When writing to Leo to advise it of the complaint, the Authority asked it to consider the requirements of Clauses 2, 3.2, 7.2, 9.1 and 29.

RESPONSE

Leo noted that in Section 4.4 Special warnings and precautions for use, the Protopic SPCs stated that exposure of the skin to sunlight should be minimised and submitted that given what the model was wearing, a short-sleeved shirt, denim jeans and boots, his skin exposure was more than adequately minimised and, as per the requirements of the SPC, could be considered to be in accordance with 'covering of the skin with appropriate clothing'.

Leo noted that the SPC did not state that exposure of the skin to sunlight should or must be avoided, and there were no contraindications in Section 4.3 around the use of the product on sun exposed skin. In fact, Section 4.2 stated: 'Protopic ointment may be used on any part of the body, including face, neck and flexure areas, except on mucous membranes'. Based on such broad applicability of the product to areas which could not easily be covered and without a stated requirement to prevent exposure to sunlight following application, there was no detrimental effect on patient safety by using such a scene; moving out of stormy to settled conditions. Leo submitted that the setting simply pictorially represented the disruption to the patient inappropriate continued use of topical corticosteroids might have.

In Leo's view, to state that the man was 'demonstrably tanned' was a matter of opinion and subjective. Based on the impression given by the man's features (brown eyes and dark hair) it was more reasonable to assume that he was of Middle Eastern heritage with a Fitzpatrick skin type of IV, as an estimate. Irrespective of which side of the photograph was considered, it was not possible to state he was 'now' tanned, as his arms were covered and he was walking in stormy conditions, sheltered by an umbrella with little to no sunlight and little in the way of any light.

Leo noted the complainant's submission that 'there is sun in the image on the right'. The image in question was created in a studio and not outside in natural conditions. As such, artificial lighting might create areas which appeared to high-light (or possibly cause shine as in this case) and shadow the feature of any shoot. If the sun was shining and temperatures were excessive, the expectation would be that the subject would be perspiring and not exhibiting shine.

Leo stated that sun, sunshine or rays of sunlight were not included in the finished image. Based on the position of the clouds and level of lighting, the scene more likely depicted late afternoon prior to sunset. However, if in this artificial situation, inclusion of the sun was to be a matter for consideration, as the light was not directly above the image, but to the right, then that would not depict midday sun and would not correlate with the position of the sun during the hours of 11am to 3pm when the sun was at its strongest and as per current British Skin Foundation and NHS guidance, the time to stay in the shade.

Leo stated that it could also be argued that although the model had changed from a long sleeved shirt to a short-sleeved one, there was no other interpretation that the primary sites, which would be prone to burning (shoulders) and predominant sites for atopic dermatitis (back, torso and legs) were covered. Additionally, it would not be unreasonable to expect him to have appropriately applied an SPF 30+ prior to going outside (either autonomously or following the advice from his physician). The shot also saw him carrying an umbrella, albeit a different one; one for which could be used to create the necessary shade during time spent outdoors, such as those for golf with UV protection.

With regard to Clause 3.2, Leo noted that the Protopic SPC stated that 'Physicians should advise patients on appropriate sun protection methods, such as minimisation of the time in the sun, use of a sunscreen product and covering of the skin with appropriate clothing.' Whilst Leo considered that inclusion of such advisory wording was warranted and was the requirement of an inherited undertaking (Case AUTH/2418/7/11) when promoting Protopic using images such as hot and sunny beaches with models in swimwear, the model, setting and overall image now in question did not. As noted above, the scene conveyed moving out of stormy to settled conditions and pictorially represented the disruption patients might experience with inappropriate, continued use of topical corticosteroids. Contrary to the allegation, the image was consistent with the SPC, specifically relating to the requirements of Section 4.4 'Special warnings and precautions for use'. All advertisements were accompanied by prescribing information for which the wording 'Minimise exposure of the skin to sunlight' was contained within.

Leo Pharma denied a breach of Clause 3.2.

With regard to Clause 7.2 Leo stated that the image was not inconsistent with the requirements of the SPC for the reasons given above. The model had not exposed his shoulders or legs and from the attire he wore, he was appropriately covered. In line with the content contained within the SPC, the use of the model and the setting to depict moving on from topical corticosteroids, as explained in detail, could not be construed as misleading with respect to patient safety. As such, Leo denied a breach of Clause 7.2.

With regard to the requirements of Clause 29 'Compliance with Undertakings', the undertaking in relation to Case AUTH/2418/7/11 was given by Astellas Pharma prior to being divested to Leo Pharma in 2018. Unfortunately, the image in question (ref PRO11003UK) was not available

to Leo to enable a detailed comparison to be undertaken nor to be supplied as part of its response.

Leo stated that however, from the descriptions in the complainant's letter and those contained within the case report, there was sufficient detail for Leo to confidently assess that the scenes used in the advertisements and their rationales were fundamentally different. Case AUTH/2418/7/11 centred around a lady dressed minimally in a vest top, shorts and sandals, with emphasis around being flare-free over a 'British summer' whereas the current Leo-produced scene accompanied the title 'Moving beyond topical corticosteroids in moderate to severe atopic dermatitis' and was concerned with raising awareness of treating patients where previous agents (topical corticosteroids) had failed or were unsuitable; as illustrated by the patient walking around in circles before progressing to the next tier of or alternative treatment. There was no reference to any season or suitability of the use of the product during the summer months, hence there was no requirement to acknowledge the warning in the SPC.

Leo denied a breach of the undertaking (Clause 29).

PANEL RULING

The Panel noted the image in question featured, on the left-hand side, a man wearing a long-sleeved shirt and trousers, who appeared to be walking in circles in the rain, holding an open umbrella; the left-hand side of the image appeared to be in dark, stormy conditions. The right-hand side of the image depicted the same man walking out of the rain and into brighter weather, with blue skies and his umbrella closed, and now wearing a short-sleeved shirt and trousers. The man was thus wearing less clothing and consequently exposing more skin than in the left-hand side of the image. The image was overlaid with the Protopic product logo and the claim 'Protopic Moving beyond topical corticosteroids in moderate to severe atopic dermatitis'.
The Panel noted that Section 4.4 (Special warnings and precautions for use) of the Protopic SPCs stated, *inter alia*:

> 'Exposure of the skin to sunlight should be minimised and the use of ultraviolet (UV) light from a solarium, therapy with UVB or UVA in combination with psoralens (PUVA) should be avoided during use of Protopic ointment (see section 5.3). Physicians should advise patients on appropriate sun protection methods, such as minimisation of the time in the sun, use of a sunscreen product and covering of the skin with appropriate clothing. Protopic ointment should not be applied to lesions that are considered to be potentially malignant or pre-malignant.'

The Panel noted Leo's submission that sunshine was not included in the finished image and that based on the position of the clouds and level of lighting, the scene more likely depicted late afternoon prior to sunset. The Panel noted, nonetheless, that the image showed blue skies and the skin would be exposed to sunlight in such conditions.

The Panel noted Leo's submission that the Protopic SPC did not state that exposure of the skin to sunlight should or must be avoided, and there were no contraindications in Section 4.3 of the SPC around the use of the product on sun exposed skin. The Panel further noted Leo's submission that Section 4.2 of the SPC stated that 'Protopic ointment may be used on any part of the body, including face, neck and flexure areas, except on mucous membranes' and that based on such broad applicability of the product to areas which cannot easily be covered and without a stated requirement to prevent exposure to sunlight following application, there was no

detrimental effect on patient safety by using the image in question which depicted moving from stormy to settled conditions.

However, the Panel noted that the Protopic patient information leaflet stated: 'If you spend time outdoors after applying Protopic, use a sunscreen and wear loose fitting clothing that protects the skin from the sun. In addition, ask your doctor for advice on other appropriate sun protection methods'.

Whilst the Panel acknowledged that patients treated with Protopic would not entirely avoid being outdoors, it was concerned that there was a clear contrast in the images before and after treatment which showed a man who had changed from a long sleeve to a short sleeve top and had closed his umbrella when walking into better and brighter weather conditions; the Panel considered that this implied that the patient did not have to be concerned about exposure to sunlight whilst on treatment and that was not so. The Panel considered that this was inconsistent with the particulars listed in the Protopic SPC and a breach of Clause 3.2 was ruled.

The Panel considered that Leo had failed to maintain high standards in this regard and a breach of Clause 9.1 was ruled.

In the Panel's view, the image on the right did not show the model as 'demonstrably tanned compared to the picture of him on the left-hand side' as alleged and therefore the Panel did not consider that the image was misleading on the narrow point alleged; no breach of Clause 7.2 was ruled in that regard.

The Panel noted in Case AUTH/2418/7/11, Astellas was ruled in breach of Clause 3.2 as the Panel in that case considered that the front cover of a Protopic leavepiece, which depicted a woman wearing less clothing and consequently exposing more skin than those around her, implied that the patient did not have to be concerned about exposure to sun which was not so and was inconsistent with the particulars listed in the Protopic SPC, which was upheld on appeal. Astellas' undertaking was signed in October 2011 which was prior to Protopic being divested to Leo Pharma in 2018.

The Panel noted that Clause 29 stated that when an undertaking had been given in relation to a ruling under the Code, the company concerned must ensure that it complied with that undertaking. The Panel noted that the undertaking for Case AUTH/2418/7/11 had been provided by Astellas. The Panel noted Leo's submission in relation to an 'inherited undertaking'. The Panel considered that Leo, following the divestment, in addition to its general responsibility for complying with the Code might have a responsibility to ensure that similar breaches of the Code in relation to Protopic were avoided. On the evidence before it, the Panel considered that it appeared that the matter at issue in the case concerning Leo ruled in breach was sufficiently similar to that which had been ruled in breach in Case AUTH/2418/7/11. The question now to be considered was whether the requirements of the Code in relation to complying with an undertaking applied to this unusual situation. On balance, the Panel decided that the requirement in the Code applied to the company concerned and thus ruled no breach of Clause 29 of the Code as that undertaking was given by Astellas and not Leo.

In the Panel's view, as it had ruled no breach of Clause 29 of the Code in relation to the alleged breach of undertaking, there could be no breach of Clause 2 of the Code in this regard. The

Panel considered, however, that the similar nature of the breaches meant that high standards had not been maintained and thus ruled a breach of Clause 9.1 of the Code in this regard.

2 Statement 'Protopic Moving beyond topical corticosteroids in moderate to severe atopic dermatitis'

COMPLAINT

The complainant alleged that the statement was misleading and the promotion was inconsistent with the SPC as the phrase 'moving beyond' implied that Protopic was more efficacious or advanced than topical corticosteroids, yet the SPC did not support that claim. The claim had not been referenced so the information was not sufficiently complete to enable the reader to assess the credibility of this information for themselves.

When writing to Leo to advise it of the complaint the Authority asked it to consider the requirements of Clauses 2, 3.2, 7.2, 7.4, 7.6 and 9.1.

RESPONSE

Leo reiterated that the focus of 'Moving beyond topical corticosteroids in moderate to severe atopic dermatitis' was the treatment of patients in whom previous topical corticosteroids had failed and were suitable for progression to the next tier of or alternative treatment. Contrary to the allegation, the title was in accordance with the terms of the Protopic marketing authorisation and was not inconsistent with the particulars of the SPC. Leo disagreed with the complainant and submitted that the phrase appropriately reflected the patient group suitable for Protopic treatment. It was clearly stated in Section 4.1 of the SPC that Protopic was indicated for 'Treatment of moderate to severe atopic dermatitis in adults who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids.'
With regard to Clause 7.2, Leo stated that 'Moving beyond…' was not a comparative claim and did not directly or indirectly claim that Protopic was more efficacious or advanced compared with topical corticosteroids. It was a reflection of the indication as listed in Section 4.1 of the SPC. Hence, Leo did not agree that the claim was either misleading or that it claimed that Protopic was more efficacious or advanced than topical corticosteroids and it denied any subsequent breach of Clause 7.2.

Leo submitted that the intention behind the 'Moving beyond…' title in the 'At a glance' page was to inform the reader that Protopic was not a first line treatment but rather one to be used where other agents such as topical corticosteroids had failed or were deemed unsuitable. Leo considered it was appropriately and adequately substantiated by the indication in Section 4.1 of the SPC.

Leo submitted that there was no requirement to reference published studies as the statement related to the indication for Protopic which was contained within and thus supported by reference to the SPC.

Leo denied all allegations relating to Clauses 3.2, 7.2, 7.4 and 7.6.

PANEL RULING

The Panel noted Leo's submission that Protopic was indicated for the treatment of moderate to severe atopic dermatitis in adults who were not adequately responsive to or were intolerant of conventional therapies such as topical corticosteroids and that the focus of the claim 'Moving beyond topical corticosteroids in moderate to severe atopic dermatitis' was the treatment of patients in whom previous topical corticosteroids had failed and were suitable for progression to the next tier of or alternative treatment.

The Panel considered that the expression 'moving beyond' was ambiguous. However, in the Panel's view, the claim did not imply that Protopic was more efficacious or advanced compared to topical corticosteroids as alleged. The Panel considered that the complainant had not discharged his/her burden of proof that the claim was inconsistent with the SPC, misleading or incapable of substantiation as alleged and based on the narrow allegation the Panel ruled no breach of Clauses 3.2, 7.2 and 7.4.

The Panel noted Leo's submission that there was no requirement to reference the statement in question to published studies as it related to the indication for Protopic which was contained within and thus supported by reference to the SPC. The Panel considered that the complainant had not discharged his/her burden of proof that the statement needed to be referenced to a published study and no breach of Clause 7.6 was ruled. The complainant had not established that Leo had failed to maintain high standards and no breach of Clause 9.1 was ruled. The Panel consequently ruled no breach of Clause 2.

3 Claim 'Protopic is designed for moderate to severe [atopic dermatitis]'

This claim was referenced to the Protopic SPC and appeared above an image of a patient scratching an apparently inflamed arm and a section of the skin.

COMPLAINT

The complainant alleged that the claim was inconsistent with the SPC which stated that Protopic could be used for flare treatment in adults and adolescents (16 years of age and above) in the treatment of moderate to severe atopic dermatitis who were not adequately responsive to or intolerant of conventional therapies such as topical corticosteroids. Therefore, Protopic should not be promoted or used as a first-line agent in moderate to severe atopic dermatitis as suggested and was only suitable for a particular population at a certain dosage for a particular length of time. The complainant stated that this broad claim was misleading and prejudiced patient safety by failing to provide prescribers with up-to-date and a balanced overview of the information.

When writing to Leo to advise it of the complaint the Authority asked it to consider the requirements of Clauses 2, 3.2, 7.2 and 9.1.

RESPONSE

Leo stated that it failed to see how 'Protopic is designed for moderate to severe [atopic dermatitis]' would suggest promotion of first line usage. The indication for the use of Protopic in the treatment of flares was stated from the outset. There was no promotion of or 'suggestion' of first line use in the claim; the claim was reflective of the applicable patient group. Leo submitted that 'designed' was not synonymous with 'indication' but rather, as per the objective of the piece, provided an easy to navigate snapshot of the severity of disease the treatment was used

for. The claim was a top-line heading for an artist's illustration explaining the principles behind the product's mode of action for the severity of atopic dermatitis it was indicated for; it quickly informed reader that it was not suitable for patients with mild atopic dermatitis, hence patients with mild disease were excluded. As such, Leo did not agree that the claim was in breach of Clause 3.2.

Leo did not consider that the claim was broad or misleading and the complainant had failed to specify how it prejudiced patient safety. The claim was a brief explanation to accompany the artist's illustrations and could not be considered in isolation of the remainder of the components. Leo did not consider that there had been a breach of Clause 7.2.

PANEL RULING

The Panel noted Leo's submission that before accessing the 'At a glance' web page at issue, readers were presented with the product's indication for the treatment of flares on the preceding 'Treatments' page as follows:

> 'Protopic® is a non-steroid ointment recommended for the treatment of moderate to severe atopic dermatitis in patients who are not responsive to or are intolerant of topical corticosteroids. It comes in two strengths:
> • 0.1%: For adults and adolescents ≥ 16 years
> • 0.03%: For adults, adolescents and children ≥ 2 years'

The Panel noted that below the indication were two tabs: 'At a glance' and 'Prescribing information'. The Panel noted Leo's submission that clicking 'At a glance' took the health professional to the webpage at issue entitled 'Moving beyond topical corticosteroids in moderate to severe atopic dermatitis'. Further below was the claim at issue 'Protopic is designed for moderate to severe AD [atopic dermatitis]'. The Panel noted Leo's submission that the claim was a top-line heading for an artist's illustration explaining the principles behind the product's mode of action for the severity of atopic dermatitis it was indicated for.

The Panel considered the content and layout of the 'at a glance' webpage and how the website was navigated. The Panel noted that the Protopic indication was not stated on the 'at a glance' webpage at issue but the indication for flare treatment was stated on the preceding webpage which provided the link to the 'at a glance' webpage. It was not clear to the Panel if the webpage at issue could be accessed directly from a search or from a link on another webpage; Leo made no submission in that regard.

The Panel was not an investigatory body; it made its rulings on the evidence provided by both parties. It appeared to the Panel that health professionals would likely access the 'at a glance' webpage from the 'treatments' page, which stated that Protopic was for patients with moderate to severe atopic dermatitis who were not responsive to or were intolerant of topical corticosteroids, and therefore would not be misled that the claim 'Protopic is designed for moderate to severe AD [atopic dermatitis]' incorrectly implied that it could be used as a first-line agent as alleged. Although it would have been helpful if the full indication for Protopic was stated on the 'at a glance' webpage, the Panel considered that the complainant had not established that the claim 'Protopic is designed for moderate to severe AD [atopic dermatitis]' in the context of the webpage and website was inconsistent with the SPC or misleading as alleged and no breach of Clauses 3.2 and 7.2 were ruled. The complainant had not established that

Leo had failed to maintain high standards in this regard and no breach of Clause 9.1 was ruled. The Panel consequently ruled no breach of Clause 2.

4 Claim 'Protopic targets inflammation + Protopic supports repair of skin barrier'

The first part of the claim about inflammation was referenced to the Protopic SPC and the second part of the claim was referenced to Xhauflaire-Uhodae *et al* (2007). The claim appeared below the drawing of a patient scratching an apparently inflamed arm and of a cross-section of the skin.

COMPLAINT

The complainant stated that for the claim that Protopic targeted inflammation, the data in the SPC was limited to *in vitro* human cells and animal models and could not be extrapolated to the clinical setting. The claim was not consistent with the SPC which stated:

'The mechanism of action of tacrolimus in atopic dermatitis is not fully understood. While the following have been observed, the clinical significance of these observations in atopic dermatitis is not known.

Via its binding to a specific cytoplasmic immunophilin (FKBP12) tacrolimus inhibits calcium dependent signal transduction pathways in T cells, thereby preventing the transcription and synthesis of IL-2, IL-3, IL-4, IL-5 and other cytokines such as GM-CSF, TNF—alpha and IFN gamma).

In vitro, in Langerhans cells isolated from normal human skin, tacrolimus reduced the stimulatory activity towards T cells. Tacrolimus has been shown to inhibit the release of inflammatory mediators from skin mast cells, basophils and eosinophils.
In animals, tacrolimus ointment suppressed inflammatory reactions in experimental and spontaneous dermatitis models that resemble human atopic dermatitis. Tacrolimus ointment did not reduce skin thickness and did not cause skin atrophy in animals.

In patients with atopic dermatitis improvement of skin lesions during treatment with tacrolimus ointment was associated with reduced Fc receptor expression on Langerhans cells and a reduction of their hyper stimulatory activity towards T cells. Tacrolimus ointment does not affect collagen synthesis in humans'.

The complainant stated that care must be taken with the use of such *in vitro* data so as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance. The wording from the SPC clearly did not support a claim that Protopic targeted inflammation in a clinical setting, was misleading and not capable of substantiation.

For the second half of the claim, the complainant noted that Xhauflaire-Uhodae *et al* was a 21 patient study with two comparator arms with the aim to assess the water content and the rate of accumulation in the stratum corneum of atopic patients using an indirect electromagnetic method while on tacrolimus or betamethasone valerate treatment. The study was not statistically powered to support such a claim nor did the study make a conclusion that Protopic supported skin barrier repair. The complainant alleged that the claim was unfair, misleading and not capable of substantiation.

When writing to Leo to advise it of the complaint the Authority asked it to consider the requirements of Clauses 2, 3.2, 7.2, 7.4 and 9.1.

RESPONSE

Leo stated that as explained in point 3 above, the claim in question supported a cartoon-like illustration of the basic principles as to how Protopic worked. No data, clinical or otherwise, was presented; basic sketches were presented to show itching and resulting inflammation in conjunction with a crude cross section of the skin.

Leo stated that atopic dermatitis was a chronic skin disease in which the skin became inflamed, causing itchiness, redness, swelling, cracking, weeping, crusting, and scaling. The inflammation was caused by activation of the immune system though the reason for the activation was unknown. Tacrolimus ointment suppressed the immune system and the inflammation by inhibiting an enzyme (calcineurin) crucial for the multiplication of T-cells, cells that were required for activation of the immune system (Hultsch *et al* 2005).

Atopic dermatitis was an inflammatory skin disease which arose as a result of immune system and skin barrier defects. Short courses of topical corticosteroids were effective treatments for atopic dermatitis; prolonged use was associated with skin barrier damage. Topical calcineurin inhibitors (including Protopic) were alternative immune-modulating treatments for atopic dermatitis purported to have no negative effects on the skin barrier (Danby *et al* 2014).

Leo noted that as per Section 5.1 of its SPC, the efficacy and safety of Protopic was assessed in more than 18,500 patients treated with tacrolimus ointment in Phase I to Phase III clinical trials. Several of those trials included as a primary end-point, response rate defined as the proportion of patients with at least 60% improvement in the modified Eczema Area and Severity Index (mEASI) between baseline and a specified time point.

Such a severity score was the sum of the intensity scores for four signs. The four signs were:

1. Redness (erythema, inflammation)
2. Thickness (induration, papulation, swelling—acute eczema)
3. Scratching (excoriation)
4. Lichenification (lined skin, furrowing, prurigo nodules—chronic eczema).

The average intensity of each sign in each body region was assessed as: none (0), mild (1), moderate (2) and severe (3).

In a six-month, multicentre, double-blind, randomised trial, 0.1% tacrolimus ointment was administered twice-a-day to adults with moderate to severe atopic dermatitis and compared to a topical corticosteroid based regimen (0.1% hydrocortisone butyrate on trunk and extremities, 1% hydrocortisone acetate on face and neck). The response rate in the 0.1% tacrolimus group was significantly higher than that in the topical corticosteroid group (71.6% vs 50.8% respectively; $p<0.001$).

Based on the modified Eczema Area and Severity Index 60 response rate, which includes a measure of inflammation, Protopic had demonstrated clinical evidence as to its effect on inflammation supported by the SPC. As such, Leo failed to see how the use of the diagram and associated claim was inconsistent with the content of the SPC or in breach of Clause 3.2.

Leo submitted that although the complainant considered that Xhauflaire-Uhodae *et al* was insufficiently powered to support the reparatory effects of Protopic on the skin barrier, Danby *et al* had shown improved skin barrier function after treatment with tacrolimus in quiescent atopic dermatitis and might therefore suggest a direct effect on the skin barrier resulting from an action of TCI other than their anti-inflammatory and immune-modulating properties. Further to that, in respect of skin barrier function, Protopic had been shown to reduce protease activity, improve collagen synthesis and skin thickness as well as improve skin hydration, pH and improve stratum corneum integrity (Chittock et al 2015 and Kyllonen *et al* 2004)

Leo stated that it disagreed with the complainant's assertion as to the suitability of the support provided by Xhauflaire-Uhodae *et al* in relation to a sketch diagram, which was one of a number of publications available discussing the positive effects of tacrolimus on skin barrier integrity.

Leo stated that in accordance with the data contained within Section 5.1 of the SPC and as outlined in detail above, based on the simplicity of the illustration and a lack of any data, *in vitro* or the like presented to accompany the figure, there had not and could not be any attempt to '... mislead as to its significance'. As a result, no extrapolation '…of such data to the clinical situation' had been made. Consequently, there was no breach of Clause 7.2.

Leo submitted that as per the detailed explanation given above, substantiation of the sketch illustration and accompanying copy was supported by the data in Section 5.1 of the SPC as well as by Xhauflaire-Uhodae *et al*. As such, Leo refuted the allegation of a breach of Clause 7.4.

PANEL RULING

The Panel noted there were illustrations of an arm being scratched and a cross-section of the skin, beneath which was the claim 'Protopic targets inflammation[1] + Protopic supports repair of skin barrier[2]'.

The Panel noted that the claim 'Protopic targets inflammation' was referenced to the Protopic SPC. The Panel noted that Section 5.1 of the SPC (Pharmacodynamic properties) stated under the subheading 'Mechanism of action and pharmacodynamic effects', *inter alia*:

> 'The mechanism of action of tacrolimus in atopic dermatitis is not fully understood. While the following have been observed, the clinical significance of these observations in atopic dermatitis is not known.
>
> …
>
> Tacrolimus has also been shown to inhibit the release of inflammatory mediators from skin mast cells, basophils and eosinophils. In animals, tacrolimus ointment suppressed inflammatory reactions in experimental and spontaneous dermatitis models that resemble human atopic dermatitis.'

The Panel noted that the supplementary information to Clause 7.2 of the Code stated, *inter alia*, that the use of data derived from in-vitro studies, studies in healthy volunteers and in animals was an area where particular care should be taken by companies and that care must be taken with the use of such data so as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there is data to show that it is of direct relevance and significance.

The Panel noted Leo's submission that as per Section 5.1 of the SPC, the efficacy and safety of Protopic was assessed in more than 18,500 patients treated with tacrolimus ointment in Phase I to Phase III clinical trials and that several of those trials included as a primary end-point, response rate defined as the proportion of patients with at least 60% improvement in the modified Eczema Area and Severity Index between baseline and a specified time point. Such a severity score was the sum of the intensity scores for four signs which were: Redness (erythema, inflammation), Thickness (induration, papulation, swelling—acute eczema), Scratching (excoriation) and Lichenification (lined skin, furrowing, prurigo nodules—chronic eczema). The Panel further noted Leo's submission that based on the modified Eczema Area and Severity Index 60 response rate, which included a measure of inflammation, Protopic had demonstrated clinical evidence as to its effect on inflammation.

The Panel considered that the complainant had not discharged his/her burden of proof that the claim 'Protopic targets inflammation' was inconsistent with the SPC, misleading or incapable of substantiation as alleged and the Panel therefore ruled no breach of Clauses 3.2, 7.2 and 7.4.

The Panel noted that the claim 'Protopic supports repair of skin barrier' was referenced to XhauflaireUhodaE *et al*.

The Panel noted that XhauflaireUhodaE *et al* was a double-blind randomised study in 21 patients with moderate atopic dermatitis affecting both forearms and assessed the comparative effect of tacrolimus and betamethasone valerate on the passive sustainable hydration of the stratum corneum. The authors of the study stated that during treatment, both compounds yielded a similar improvement in skin barrier function.

The Panel further noted Leo's submission that Danby *et al* (2014) had shown improved skin barrier function after treatment with tacrolimus in quiescent atopic dermatitis. The Panel noted that Danby *et al* compared the effects of betamethasone valerate 0.1% cream and tacrolimus 0.1% ointment on the skin barrier in 20 volunteers with quiescent atopic dermatitis. The authors concluded that tacrolimus 0.1% ointment improved the condition of the skin barrier.

The Panel noted that the claim at issue was not comparing Protopic to any other treatment. The claim stated 'Protopic supports repair of skin barrier'. The Panel considered, on the evidence before it, that the complainant had not discharged his/her burden of proof that the claim 'Protopic supports repair of skin barrier' was misleading or incapable of substantiation as alleged and the Panel therefore ruled no breach of Clauses 7.2 and 7.4.

The Panel consequently ruled no breach of Clauses 9.1 and 2.

5 'Help patients know what to expect when they start treatment with Protopic' and patient 'before and after' photographs

This statement appeared above two pairs of patient photographs showing baseline appearance of the skin and then after 4 weeks' treatment on the face and chest.

COMPLAINT

The complainant alleged that the statement 'Help patients know what to expect when they start treatment with Protopic implied that the page or at least that section of the page should be used by a health professional in a patient consultation as a visual aid. Therefore the information for

patient consultation should contain the mandatory wording for patients using a medicine as per the Code which it did not.

The complainant alleged that such information for consultation with patients should not be a part of a promotional webpage which in turn promoted the product to the public.

The complainant further noted that the clinical images were labelled as being taken at baseline and 'After 4 weeks' but there was no information provided as to whether the patient was treated with Protopic for an initial flare or was on maintenance therapy as the posology varied accordingly. The complainant alleged that the information on the product was ambiguous and incomplete.

The complainant noted that for flare treatment, the SPC recommended that if no signs of improvement were seen after two weeks of treatment, further treatment options should be considered. The complainant submitted that the inclusion of a baseline and 4 week image suggested that Protopic should be used for 4 weeks and then assessed, which was misleading. As a result of the use of these timepoints, a patient prescribed Protopic for flare treatment might be left on treatment beyond the two week point at which it should be assessed, and assessment might take place after 4 weeks to see if there was improvement. The complainant alleged that the incomplete and selective information prejudiced patient safety. These clinical images did not promote the rational use of a medicine as patients might be left on Protopic unnecessarily and for longer than appropriate.

When writing to Leo to advise it of the complaint the Authority asked it to consider the requirements of Clauses 2, 3.2, 7.2, 7.10, 9.1, 26.1 and 26.3.

RESPONSE

Leo stated that the images presented were before and after photographs of two patients, the intention of which was to be an educational guide for prescribers only and not to be presented to patients. No direction was given to the clinician to show the images to patients, simply a suggestion of how to communicate what patients could expect after treatment with Protopic. The audience to whom the information was directed was clearly stated at the top of the page: 'This site is indicated only for healthcare professionals resident in the United Kingdom or Ireland'.

Leo reiterated that there was no direction given anywhere on the page to clinicians to use the images in an in-clinic demonstration with their patients. As such, there was no attempted suggestion of promotion of Protopic to the public and the complainant had failed to demonstrate where such a breach had actually occurred.

Leo stated that as the material was not intended for patients, the statement relating to side effects required as per Clause 26.3 was not, and would not be, included. The adverse event reporting requirement for clinicians under Section 4.9 had been included as the item was intended for clinicians as denoted by inclusion of 'This site is indicated only for healthcare professionals resident in the United Kingdom or Ireland' at the outset.

As such, Leo rejected any suggestion that the webpage was in breach of Clauses 26.1 or 26.3.

Leo submitted that the objective of the piece was to illustrate the treatment of flares as exemplified by the wording 'Help patients know what to expect when they start treatment with Protopic'. Use of the word, 'Start' clearly demonstrated that the adult patient to be considered for treatment had had no prior exposure to the product. Hence, the dose regimen could only be that for the treatment of flares.

With regard to the complainant's concern that a patient might be left on treatment beyond the two week point at which it should be assessed Leo noted that the SPC actually stated that 'Generally, improvement is seen within one week of starting treatment. If no signs of improvement are seen after two weeks of treatment, further treatment options should be considered'. This was a suggested timepoint for assessment only and did not state that Protopic was to be stopped. Leo submitted that the complainant had failed to include that the SPC first stated 'Treatment should be started with Protopic 0.1% twice a day and treatment should be continued until clearance of the lesion.'

As per Section 5.1 of the SPC, in a six-month multicentre double-blind randomised trial, 0.1% tacrolimus ointment was administered twice a day to adults with moderate to severe atopic dermatitis and compared with a topical corticosteroid based regimen (0.1% hydrocortisone butyrate on trunk and extremities, 1% hydrocortisone acetate on face and neck). The primary endpoint was the response rate at 3 months defined as the proportion of patients with at least 60% improvement in the modified Eczema Area and Severity Index between baseline and month 3. As such, it was neither unreasonable nor misleading to present results of treatment with Protopic after 4 weeks.

The clinical images presented demonstrated that in the patients shown, the product had been efficacious as exemplified by the images taken at week 4.

Leo stated that the aim of the material was to provide a brief summation of Leo's products. Unfortunately, from the complainant's perspective, the majority of the content of the SPC would be required to be presented to satisfy his/her subjective interpretation of the material, which was not a reasonable expectation.

With regard to Clause 3.2 and as explained above, Leo stated that presentation of patient images at week 4 was not inconsistent with the particulars of the SPC, which stated that 'Treatment should be started with Protopic 0.1% twice a day and treatment should be continued until clearance of the lesion.' Further, the response rate at 3 months was used as a primary endpoint in a Protopic registration study.

Leo contended that the images were consistent with the requirements of the SPC as explained above. Rather than being subjectively assessed as misleading, Leo considered that they were a fair reflection of the results of Protopic use as prescribed by the clinician.

Leo considered that presentation of images to show the results of Protopic use after 4 weeks complied with the requirement to encourage the rational use of a medicine. In accordance with the requirements of the SPC, it would not be unreasonable to present the results of treatment after 3 months, as supported by the clinical data in Section 5.1, but also as per Section 4.1 'Treatment should be started with Protopic 0.1% twice a day and treatment should be continued until clearance of the lesion.'

Leo denied breaches of Clause 2, 3.2, 7.2, 7.10 and 9.1.

PANEL RULING

The Panel noted that beneath the heading 'Protopic efficacy in action' was the statement 'Help patients know what to expect when they start treatment with Protopic' which was placed above two pairs of photographs showing before and after 4 weeks of treatment.

The Panel noted that the photographs were on a website intended for health professionals and, in the Panel's view, were for health professionals to understand what to expect following treatment so that they could explain this to their patients. Consequently, the Panel did not consider that the images promoted a prescription only medicine to the public or were for viewing by the public and therefore no breach of Clauses 26.1 and 26.3 were ruled. The Panel consequently ruled no breach of Clauses 9.1 and 2 in this regard.

The Panel noted that section 4.2 (Posology and method of administration) of the Protopic SPC stated: 'Generally, improvement is seen within one week of starting treatment. If no signs of improvement are seen after two weeks of treatment, further treatment options should be considered.' The Panel further noted that the SPC stated, for adults and adolescents (16 years of age and above), 'Treatment should be started with Protopic 0.1% twice a day and treatment should be continued until clearance of the lesion.'

The Panel did not consider that the complainant had established that photographs depicting results after 4 weeks of treatment, in the material at issue, meant that Protopic had been promoted in a manner inconsistent with its SPC as alleged and no breach of Clause 3.2 was ruled. Nor did the Panel consider that the photographs were misleading or did not promote the rational use of the medicine as alleged and no breach of Clauses 7.2 and 7.10 were ruled. The Panel consequently ruled no breach of Clauses 9.1 and 2 in this regard.

6 Lack of warning regarding sun protection methods

COMPLAINT

The complainant noted that under the heading 'Preparing your patients for their Protopic 0.1% treatment' was a mention of skin irritation, burning sensation and pruritis but there was no wording to reflect the warning from Section 4.4 of the SPC, 'Physicians should advise patients on appropriate sun protection methods such as minimisation of the time in the sun, use of a sunscreen product and covering of the skin with appropriate clothing'. This wording about burning sensation etc was to the left of an outline sketch of a woman with short hair in a short sleeveless dress with exposed arms, legs and neck. The complainant alleged that the image together with the lack of information on precautions around UV exposure did not give the prescriber an accurate presentation of Protopic; it prejudiced patient safety and was misleading.

When writing to Leo to advise it of the complaint the Authority asked it to consider the requirements of Clauses 7.2, 7.9, 9.1 and 2.

RESPONSE

Leo submitted that the watercolour sketch of a lady in a white dress accompanied safety information pertinent to raising patient awareness of the potential for product application related adverse events as contained in Section 4.8 of the SPC. There was no suggestion that the illustration of the character in the sketch was, or would be, exposed to ultraviolet (UV) radiation.

Equally, UV-related adverse events were not listed in Section 4.8 of the SPC. Leo also added that there was no indication from the artist's sketch that the individual would be a candidate to consider using a solarium as per the content in Section 4.4 of the SPC.

Leo stated that the section which related to 'Preparing your patients for their Protopic 0.1% treatment', aimed to convey awareness of very commonly experienced undesirable effects to the clinician. As stated in Section 4.8 of the SPC, 'In clinical studies approximately 50% of patients experienced some type of skin irritation adverse reaction at the site of application. Burning sensation and pruritus were very common, usually mild to moderate in severity and tended to resolve within one week of starting treatment. Erythema was a common skin irritation adverse reaction'.

As detailed above, Leo submitted that it had not misled nor compromised patient safety with the use of the image and considered the alleged failure to include 'information on precautions around UV exposure' was not warranted. Leo had however, provided data to enable the physician to appropriately inform the Protopic patient of potential 'very common' application site adverse events which might arise in line with the requirements of Section 4.8.

Leo denied breaches of Clauses 7.2 and 7.9.

PANEL RULING

The Panel noted that the Code required all promotional material to include prescribing information which must contain, amongst other things, a succinct statement of common adverse reactions likely to be encountered in clinical practice, serious adverse reactions and precautions and contra-indications relevant to the indications in the advertisement, giving, in an abbreviated form, the substance of the relevant information in the SPC, together with a statement that prescribers should consult the SPC in relation to other adverse reactions.

The Panel noted that the website contained a link to the prescribing information; the Panel did not have a copy of this prescribing information before it and Leo had made no submission in that regard.

The Panel considered that whether a special warning or precaution also needed to be highlighted in another section of the promotional material depended on a consideration of all of the circumstances including the nature of the warning/precaution and the content, layout, audience and intended use of the material.

The Panel noted that next to the sketch of a lady in a short sleeveless dress and beneath the heading 'Preparing your patients for their Protopic 0.1% treatment', on a green coloured background it stated:

> '1 in 2 patients experienced some type of skin irritation at the site of application.
>
> Burning sensation and pruritus were very common and tended to resolve within one week of starting treatment.'

The Panel noted that the sketch was very basic and considered that it was difficult to tell if the individual was indoors or outdoors. In the Panel's view, this section of the material appeared to

focus on application site reactions. The Panel noted that Section 4.8 of the Protopic 0.1% SPC stated:

> 'In clinical studies approximately 50% of patients experienced some type of skin irritation adverse reaction at the site of application. Burning sensation and pruritus were very common, usually mild to moderate in severity and tended to resolve within one week of starting treatment.'

The Panel did not consider that the sketch implied that there were no concerns with sun exposure. Whilst it might have been helpful within this section of the material to include the special warning and precaution for use regarding minimising exposure of the skin to sunlight etc, the Panel did not consider that the complainant had established that its omission rendered the material misleading as alleged and no breach of Clause 7.2 was ruled.

Clause 7.9 stated that information and claims about adverse reactions must reflect available evidence or be capable of substantiation by clinical experience. It must not be stated that a product has no adverse reactions, toxic hazards or risks of addiction or dependency. The word 'safe' must not be used without qualification.

In the Panel's view, the complainant had not made an allegation in relation to Clause 7.9 and therefore no breach of Clause 7.9 was ruled.

The Panel consequently ruled no breach of Clauses 9.1 and 2.

7 Claim 'Protopic 0.1% delays time to next flare when used proactively' and associated graph

COMPLAINT

The complainant noted that the claim was used as a heading to a graph with a sub-heading to the same graph which read 'In a sub analysis of a pooled population of 153 patients with moderate to severe AD treated with tacrolimus or vehicle'. The SPC was used as a reference for both claims.

The complainant stated that the study design and primary endpoint in the study had not been included to put the claim in to context or to inform the reader that the results were in a sub-population, treated twice daily until they had reached a predefined assessment score for a maximum of 6 weeks. At 6 weeks, these patients were randomised to the study for twice weekly application and if a disease exacerbation occurred, patients were treated twice daily with tacrolimus open label for a maximum of 6 weeks until the IGA score had returned to less than or equal to 2.

The claim and graph around delaying time to the next flare when used proactively was misleading as it did not take into consideration the time taken to undergo 'reactive' management (6 weeks in this study) and before 'proactive' management could start.

The complainant noted that the associated graph depicted Vehicle and Protopic 0.1% showing time over 12 months and the time point label used was 'Median time to first disease exacerbation'. According to the graph, the median time to first disease exacerbation for Protopic was 142 days vs 15 days for the vehicle. It was stated that the graph had been

adapted from the Protopic SPC, however the numbers mentioned, 15 or 142 days referred to 'Median time to first disease exacerbation requiring substantial intervention' according to the SPC.

The complainant stated that the median time to first disease exacerbation was listed as 123 days for Protopic 0.1% and 14 days for vehicle in the SPC. The difference between 142 days and 123 days was a significant difference therefore the information in the Protopic graph exaggerated the efficacy of Protopic, was misleading, was incompatible with the SPC and was not capable of substantiation.

The complainant added that the visual of artwork itself was also misleading as it showed only one flare for Protopic over 1 year when in fact the median time to disease exacerbation was 123 days so more than one flare would be expected over 12 months.

When writing to Leo to advise it of the complaint the Authority asked it to consider the requirements of Clause 2, 3.2, 7.2, 7.4 and 9.1.

RESPONSE

Leo stated that again, an illustration had been used in keeping with the 'At a glance' brief nature of the webpage. It clearly stated that it was 'For illustrative purposes only, Adapted from Protopic Summary of Product Characteristics'. The nature of the content, as denoted by the tab that the reader clicked on to access this page, was not meant to provide a comprehensive and complete overview of the product.

Leo stated that through the title of the graph, 'Protopic 0.1% delays time to next flare when used proactively' there was no attempt to mislead the reader that Protopic could be used as a maintenance therapy. The claim was referenced to the SPC and was adequately supported by the content in Table 4 in Section 5.1, where in a sub-analysis of a pooled population of patients with moderate to severe atopic dermatitis the differences examined (such as Median time to first Disease Exacerbation) remained statistically significant. Maintenance treatment was one of the licensed indications for Protopic 0.1%, and the SPC in that regard stated 'Treatment of moderate to severe atopic dermatitis for the prevention of flares and the **prolongation of flare-free intervals** in patients experiencing a high frequency of disease exacerbations (ie occurring 4 or more times per year) who have had an initial response to a maximum of 6 weeks treatment of twice daily tacrolimus ointment (lesions cleared, almost cleared or mildly affected)' (emphasis added). Leo considered that the claim 'delays time to next flare when used proactively' was not inconsistent with the licensed indication '… prolongation of flare-free intervals' as stated in the SPC. Leo further noted that when hovering or clicking on the 12-month line, the x-axis pop-up informed the reader that the image was an 'Illustration of Protopic effectiveness and flare delay'.

Leo denied a breach of Clause 7.2.

With regard to the graph, Leo stated that on subsequent inspection of Table 4 'Efficacy (moderate to severe population)' in Section 5.1 of the SPC, it agreed that there had been an error in adequately labelling the efficacy points presented. The data points 142 v 15 days for Protopic and placebo respectively correlated with 'Median time to first disease exacerbation requiring substantial intervention' and not 'Median time to first disease exacerbation'. Leo regrettably admitted to omitting to include 'substantial intervention' but refuted the allegation that it had intentionally exaggerated the efficacy of the product.

Leo noted that the complainant considered that the difference between 142 days and 123 days (the latter figure which correlated with 'Median time to first disease exacerbation') was significant. Without inclusion of a statistical analysis on behalf of the complainant, Leo considered the allegation was without foundation and the terminology alleged by the claimant to highlight his/her complaint in turn was unsuitable.

Leo regrettably admitted to a breach of Clauses 3.2 and 7.4 due to an error in labelling and for which it unreservedly apologised. However, Leo strongly objected to any accusation that the omission was an attempt to mislead or exaggerate the results presented and was in breach of Clause 7.2. The data for Protopic presented in Table 4 of the SPC was statistically significant for Protopic vs placebo and the chart clearly stated that it had been adapted from the SPC. The webpage had been taken down to be amended.

Whilst Leo regrettably admitted to a breach of Clause 3.2 and 7.4 due to an error in labelling, it did not consider this overall to represent a general failure to maintain high standards, or that this brought discredit upon, or reduce confidence in, the pharmaceutical industry, and therefore refute allegations of breaches of Clause 9.1 or Clause 2.

With regard to the complainant's final point, Leo noted that the primary endpoint in the six-month multicentre double-blind randomised trial, where 0.1% tacrolimus ointment was administered twice a day to adults with moderate to severe atopic dermatitis and compared to a topical corticosteroid based regimen (0.1% hydrocortisone butyrate on trunk and extremities, 1% hydrocortisone acetate on face and neck) was the number of disease exacerbations requiring a 'substantial therapeutic intervention' during the DCP, defined as an exacerbation with an IGA of 3-5 (ie moderate, severe and very severe disease) on the first day of the flare, and required more than 7 days treatment. The study showed significant benefit with twice weekly treatment with tacrolimus ointment with regard to the primary and key secondary endpoints over a period of 12 months in a pooled population of patients with mild to severe atopic dermatitis. In a sub-analysis of a pooled population of patients with moderate to severe atopic dermatitis these differences remained statistically significant.

Table 4 in Section 5.1 of the SPC showed the median number of disease exacerbations adjusted for time at risk as 1.0 and 6.8 for Protopic and placebo vehicle respectively over the 12 month study period. These figures had been presented in the graph in question over the 12-month period as stated.

As such, Leo considered there had been no breach of Clause 7.2 as the data presented was not misleading and had been presented illustratively in accordance with the data contained within Section 5.1 of the SPC.

PANEL RULING

The Panel noted that Section 4.1 of the Protopic 0.1% ointment SPC stated that it was indicated in adults and adolescents (16 years of age and above) for:

> <u>Flare treatment</u>
> Treatment of moderate to severe atopic dermatitis in adults who are not adequately responsive to or are intolerant of conventional therapies such as topical corticosteroids.
>
> <u>Maintenance treatment</u>

> Treatment of moderate to severe atopic dermatitis for the prevention of flares and the prolongation of flare-free intervals in patients experiencing a high frequency of disease exacerbations (ie occurring 4 or more times per year) who have had an initial response to a maximum of 6 weeks treatment of twice daily tacrolimus ointment (lesions cleared, almost cleared or mildly affected).

The Panel noted that the webpage did not state the Protopic 0.1% indications. The preceding page which gave access to the webpage in question only gave the licensed indication for flare treatment.

The Panel noted the complainant's allegation that the claim 'Protopic 0.1% delays time to next flare when used proactively' and accompanying graph was misleading as it did not take into consideration the time taken to undergo 'reactive' management which was 6 weeks in the study.

The Panel further noted the lack of information about the study design on the webpage in question; the webpage made no reference to the fact that patients in this study had had previous treatment with tacrolimus twice daily until clear, almost clear or mild disease for a maximum of 6 weeks before being randomised to receive either tacrolimus or vehicle, once a day twice weekly. The misleading impression given of the study was compounded by the fact that the indication for Protopic 0.1% as a maintenance treatment had not been stated on the webpage in question or the preceding webpage and therefore it was not clear to health professionals reading the material that Protopic was only to be used as a maintenance therapy in patients who had had an initial response to a maximum of 6 weeks treatment of twice daily tacrolimus ointment (lesions cleared, almost cleared or mildly affected). Furthermore, the webpage did not make clear the dosing frequency (once a day twice weekly) for which the results presented were based upon. The Panel considered that the webpage had insufficient information about the study design to put the claim 'Protopic 0.1% delays time to next flare when used proactively' into context and a breach of Clause 7.2 was ruled.

The Panel noted that the graph in the material in question stated that the median time to first disease exacerbation was 15 days for vehicle and 142 days for Protopic 0.1% when in fact the SPC stated that it was 14 days vs 123 days, respectively. The Panel noted Leo's submission that this was an error in the promotional material which gave the median time to first disease exacerbation requiring substantial intervention rather than median time to first disease exacerbation as stated. The Panel considered that the error in the graph misleadingly implied that Protopic 0.1% delayed time to disease exacerbation for a longer period than the study had reported and a breach of Clause 7.2 was ruled.

The graph was inconsistent with the study data in section 5.1 of the SPC and a breach of Clause 3.2 was ruled as acknowledged by Leo. The incorrect data in the graph was incapable of substantiation and a breach of Clause 7.4 was ruled as acknowledged by Leo. High standards had not been maintained in this regard and a breach of Clause 9.1 was ruled.

In relation to the allegation about the number of flares, the Panel considered that the graph implied that patients taking Protopic 0.1% in the study had a median of 1 flare during the 12 month study period vs 6.8 flares for those patients taking the vehicle. The Panel noted that the SPC stated that the median number of disease exacerbations adjusted for time at risk was 1.0 for tacrolimus 0.1% vs 6.8 for vehicle. The Panel considered that the complainant had not established that the data regarding number of flares in the graph was misleading as alleged and no breach of Clause 7.2 was ruled.

Clause 2 was a sign of particular censure and was reserved for such use. The Panel noted its rulings of breaches of the Code above which it considered adequately covered the matter and no breach of Clause 2 was ruled.

8 Use of 0.1% Protopic

COMPLAINT

The complainant stated that Leo had only presented information on the higher strength of tacrolimus, Protopic 0.1% vs Protopic 0.03%, and its claims and clinical images would suggest it was encouraging long-term use of the product, ie proactive management of flares. There was no information to reflect the fact that the Protopic SPC stated that it was recommended to use the lowest strength and the lowest frequency for the shortest duration necessary as determined by the physician's evaluation of the clinical condition. This was due to results of long-term studies and experience; a link between Protopic ointment and malignancies had not been confirmed but definitive conclusions could not be drawn. The complainant alleged that this first line, prolonged, high strength promotion without providing relevant warnings was likely to prejudice patient safety.

When writing to Leo to advise it of the complaint the Authority asked it to consider the requirements of Clauses 2, 3.2, 7.2 and 9.1.

RESPONSE

Leo stated that it was unclear as to the basis for the allegation. Leo had not stated or suggested anywhere in the promotional offering that Protopic 0.1% should be used continuously, or long-term. In fact, from the outset, it was stated that 'Protopic treatment should be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis'.

Leo stated that whilst the lower strength preparation, 0.03%, was suitable for use in children aged 2 and above, the 0.1% was licensed only for adults and adolescents aged 16 years and above. The Code did not mandate that all products with a marketing authorisation were to be promoted. Unless the complainant could specify how long-term use of the product was being encouraged, Leo was unable to fully address the allegation and respond appropriately.

Based on the ambiguity of the complaint and in the absence of clarity as to what was being alleged, Leo refuted the allegations of breaches of Clauses 3.2 and 7.2.

PANEL RULING

The Panel noted that the Protopic 0.1% SPC stated in Section 4.2 (posology and method of administration), in relation to maintenance treatment, that after 12 months treatment, a review of the patient`s condition should be conducted by the physician and a decision taken whether to continue maintenance treatment in the absence of safety data for maintenance treatment beyond 12 months.

The Panel noted that the lower strength of Protopic, 0.03%, was referred to on the preceding list of treatments page and on the 'at a glance' page in question.

The Panel considered that the complainant had not established that the material encouraged use of Protopic 0.1% long term. Reference to its use proactively did not, in the Panel's view, imply that the medicine should be used indefinitely. The SPC and material stated that Protopic treatment should be initiated by physicians with experience in the diagnosis and treatment of atopic dermatitis. In the Panel's view, whilst it would have been helpful to have stated on the webpage the information from the SPC that in relation to maintenance treatment, after 12 months, a review of the patient should be conducted by the physician and a decision taken whether to continue maintenance treatment in the absence of safety data beyond 12 months, the Panel did not consider that the omission of this information on the webpage misleadingly implied that Protopic 0.1% should be used long-term as alleged or that promotion was inconsistent with the particulars in the SPC. No breach of Clauses 7.2 and 3.2 was ruled in that regard. Consequently, no breach of Clauses 9.1 and 2 were ruled.

9 Date of the SPC used as a reference

COMPLAINT

The complainant noted that the web page in question used the 'Protopic summary of product characteristics' as a reference. Leo had not committed itself by placing a date of last revision next to the reference. The date of the page where the information was placed was May 2019. The SPC for Protopic was updated according to medicines.org.uk in August 2020. The complainant stated that it appeared that the content of the web page was not reviewed after that update and the reference used was not clear.

When writing to Leo, the Authority asked it to consider the requirements of Clauses 2, 7.2 and 9.1.

RESPONSE

Leo stated that the web page (ref MAT-21383) was dated May 2019. The SPC was updated to include changes as highlighted by the complainant in August 2020 and the prescribing information accompanying the piece, which was available as a separate link was amended and certified in September 2020.

Leo stated that although changes were made to the SPC, inclusion of that information had no bearing on the existing content of this piece. In accordance with the requirements of Clause 14.5, 'Material which was still in use must be recertified at intervals of no more than two years to ensure that it continued to conform with the relevant regulations relating to advertising and the Code,' Leo submitted that the web page had been taken down to be amended.

Leo denied a breach of Clause 7.2.

PANEL RULING

The Panel noted Leo's submission that the changes made to the SPC in August 2020 had no bearing on the existing content of the material in question apart from the prescribing information which had been amended and separately certified in September 2020. The Panel did not have a copy of this prescribing information; Leo made no submission in that regard.

The Panel did not consider that the complainant had established that reference to the Protopic SPC on the webpage, without providing the SPC date of revision, in itself, was misleading as alleged and no breach of Clause 7.2 was ruled. The Panel consequently ruled no breach of Clauses 9.1 and 2 on this narrow point.

Overall

The Panel noted its rulings at Points 1 to 9 above and considered that its rulings adequately covered each matter and that further rulings in relation to Clauses 9.1 and 2 cumulatively were not warranted and no breach of Clause 9.1 and 2 was ruled in that regard.

Complaint received **9 April 2021**

Case completed **27 January 2022**