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Case No: HP13E02404

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Royal Courts of Justice, Rolls Building
Fetter Lane, London, EC4A 1NL

Date: 06/10/2014

Before :

MR JUSTICE BIRSS

- -

Between :

(1) TEVA UK LIMITED **(2) TEVA PHARMACEUTICAL INDUSTRIES LIMITED**	**Claimants**
- and -	
LEO PHARMA A/S	**Defendant**
- and -	
LEO LABORATORIES LIMITED	**Third Party**

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- -

Daniel Alexander QC and **Mark Chacksfield** and **Joe Delaney** (instructed by **Pinsent Masons LLP**) for the **Claimants**
Henry Carr QC and **Tom Alkin** (instructed by **Simmons & Simmons LLP**) for the **Defendant and Third Party**

Hearing dates: 15th - 18th and 21st July 2014

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Approved Judgment

I direct that pursuant to CPR PD 39A para 6.1 no official shorthand note shall be taken of this Judgment and that copies of this version as handed down may be treated as authentic.

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MR. JUSTICE BIRSS

Mr Justice Birss :

1. This case is about the treatment of psoriasis using an ointment comprising a combination of a corticosteroid such as betamethasone and a vitamin D analogue such as calcipotriol. The defendant and third party (LEO) have a successful product marketed in the UK as Dovobet Ointment. Its sales are substantial. The claimants (TEVA) wish to sell a generic version of that ointment.

2. LEO have two patents: EP 1 178 808 entitled "*Non-aqueous pharmaceutical composition for dermal use to treat psoriasis comprising a vitamin, a corticosteroid and a solvent component*" and EP 2 455 083 entitled "*Pharmaceutical composition for dermal use comprising calcipotriol and betamethasone for treating psoriasis*". The 083 patent is a divisional of the 808 patent. LEO contend that TEVA's proposed product would infringe these patents. A (confidential) product description has been provided. TEVA have no positive defence to the allegation that their product would fall within the relevant claims. TEVA contend that both patents are invalid on three grounds: obviousness, insufficiency and added matter. TEVA's obviousness case involves a single attack based on a combination of the common general knowledge and a prior US patent 4,083,974 entitled "*Topical, steroidal anti-inflammatory preparations containing polyoxypropylene 15 stearyl ether*" assigned to Upjohn naming Joseph Turi as the inventor (Turi). LEO have applied to amend the claims. LEO contend that the claims in their amended form are valid.

3. TEVA have opposed both Patents before the EPO. The 808 Patent has also been opposed by Sandoz and Pentapharma. It was subject to oral proceedings in prosecution and three rounds of third party observations. Oral proceedings are now due to be heard by the Opposition Division on 20 October 2014. The 083 Patent was opposed by TEVA, Pentafarma and Mylan in June 2014 and no oral hearing date has yet been set. There are also parallel proceedings in the USA and in Canada.

The witnesses

4. TEVA called Professor David Gawkrodger and Professor Patrick Crowley. LEO called Professor Peter van der Kerkhof and Professor Marc Brown.

5. Professor Gawkrodger is Professor Emeritus in Dermatology at the University of Sheffield having been a consultant dermatologist at the Royal Hallamshire Hospital, Sheffield from 1988 until 2012. He fully retired in 2012 and today does no clinical work. His clinical work focussed on general dermatology including all types of skin disease including psoriasis. His research interests have been wide ranging but have included some research on psoriasis although LEO are right that his research interest in psoriasis was limited.

6. LEO pointed out that Professor Gawkrodger had not worked in a drug development team whereas Professor van der Kerkhof had extensive experience in that area. I will take that into account.

7. LEO submitted that the fact Professor Gawkrodger was unfamiliar with the fact that calcipotriol was a delicate product, sensitive to degradation at the acidic pH levels at which corticosteroids are most stable and that this unfamiliarity was a result of his lack of interest in calcipotriol formulations at the time. They submitted this

reinforced the artificiality of his position in this case and showed that he had to speculate about his participation in a drug development team. The Professor was indeed unaware of these characteristics of calcipotriol but I do not accept that this means he was not in a position to help the court. His position shows that not all dermatologists knew or were interested in such characteristics. I will return to this below. As I have already said, I will take into account the different experience in drug development of the two clinical experts.

8. Professor Gawkrodger's report referred to the 1997 Guidelines on the management of psoriasis to which he had contributed. However LEO rightly pointed to an error in his report about this, for which the Professor apologised. The mistake was not deliberate but it showed that he had not checked the whole of his report as carefully as he ought to have.

9. Professor Crowley is a Visiting Professor at The School of Pharmacy, King's College, London. He founded Callum Consultancy LLC which provides consultancy services in drug development, dosage form development and regulatory filings. He retired from GlaxoSmithKline in 2008 having worked there and in its predecessor companies since starting at Beecham in 1971. His specialism was in pharmaceutical formulation development. This included some topical formulations but his experience of topical formulations is more limited than that of Professor Brown. It was put to him that he had never succeeded in producing a stable topical formulation containing more than one active ingredient, which he accepted. Nevertheless this point cannot be taken too far in the context of topical formulation development generally since many formulations attempted by Professor Brown did not succeed either.

10. LEO submitted that Professor Crowley's report contained sweeping generalisations which he was unable to maintain in cross-examination. There were specific instances of this and I will take them into account but their existence does not mean I did not find Professor Crowley's views of assistance in other areas. The specific instances were (i) the idea that pH dependent instability would simply not be an issue in a non-aqueous formulation, (ii) that apparent pH was an unknown concept and (iii) that reducing irritancy caused by propylene glycol would be a major requirement of a development project. These points are addressed further below in context but at this stage I can state that pH dependent stability will always be something for the skilled person to consider, even in a nominally non-aqueous environment; apparent pH was a concept known to topical formulators; and irritancy by propylene glycol was not regarded as significant by topical formulators. A further alleged sweeping generalisation related to the likelihood of regulatory approval for polyoxypropylene 15 stearyl ether. Again the issue is addressed below but in any case I reject this as a criticism of Professor Crowley.

11. Professor van der Kerkhof is Head of the Department of Dermatology and Venerology at the Radboud University Medical Centre (UMC), Nijmegen, The Netherlands. He became a resident in dermatology at the Radboud UMC in 1983 and has remained there ever since. As well as treating patients, Professor van der Kerkhof has worked for 30 years carrying out research into the pathogenesis and treatment of psoriasis. He has worked with a number of pharmaceutical companies in the field in relation to the development of new drugs, including LEO.

12. TEVA submitted that Professor van der Kerkhof was a cheerleader for the LEO cause and in some respects came across as promulgating the party line. I reject that criticism. The Professor gave his evidence enthusiastically, for which I am grateful. In my judgment it was a reflection of his clear and genuine passion for the subject and not a sign of a partisan witness.

13. A point arose on his opinion about the *Papp* paper on the efficacy of the formulation the subject of this action. The *Papp* paper essentially publishes the same clinical data (in more detail) as is in the patents. The paper shows that the co-formulation produces better clinical results than either monotherapy alone. In cross-examination I took Professor van der Kerkhof's opinion to be one of real surprise that a single formulation of the two compounds was possible since before he had understood it was not possible. He accepted that if the clinician assumed the co-formulation was stable, the clinical results achieved would be expected. In re-examination he emphasised that the clinical result was a new result and that to predict such a result before doing the clinical test would have been "pure speculation". I do not believe the Professor was seeking to change his evidence in a material way, he was just answering questions from a different perspective. I will return to the Professor's views below.

14. TEVA also criticised Professor van der Kerkhof for his evidence about a prejudice concerning corticosteroids. I deal with this issue below.

15. TEVA rightly pointed out that Professor van der Kerkhof was at the "top end" of specialist dermatologists and that this accounted for his negative views about combination products. I will take the Professor's professional position into account.

16. Professor Brown has held the Chair in Pharmaceutics at the School of Pharmacy at the University of Hertfordshire since 2006. He has also taken up professorships in pharmaceutics at Reading and Dundee universities. In the 1990s Professor Brown worked as a researcher at King's College, London and part time as a Director of Pharmaceutical Development in industry. In 1999 he co-founded a spin-out company called MedPharm Ltd. It is a contract research organisation specialising in the formulation of topical drug delivery systems. Today he is Chief Scientific Officer, Chief Operating Officer and a Director of MedPharm. The company has been involved in over 250 development projects out of which 16 gained regulatory approval.

17. TEVA submitted Professor Brown stuck rather rigidly to the line that "no-one would have done it" and gave what TEVA submitted was a very implausible view of formulation which envisages that formulators do not try to make formulations if asked but think of reasons not to. TEVA contended he was unprepared to contemplate considering the matter from a perspective which did not take into account regulatory considerations and that this means his evidence had to be treated with caution. I do not regard these criticisms of the Professor as fair. His evidence reflected his genuinely held opinions. A fair point taken by TEVA was that Professor Brown had said in his reports that "none of Arlamol E's properties were especially interesting". TEVA's cross-examination showed that this was an overstatement and Professor Brown accepted that.

18. Each side has criticised the experts called by the other party. None of the points I have accepted are matters of such significance that I should simply reject out of hand

the evidence of any of the experts. All four gentlemen were seeking fairly to explain the technical matters in the case and their opinions about the issues. They were seeking to help the court understand the dispute from their perspectives. I am grateful to all four of them for their evidence.

The common general knowledge and the person skilled in the art

19. In this case the person skilled in the art will be a team comprising a skilled clinician and a skilled formulator. The team may include other members but these two are the important ones in this case.

20. The common general knowledge of the skilled clinician relevant to this case includes the following matters.

21. Psoriasis is a chronic inflammatory disease relating to the skin whereby inflammation of the skin causes overproduction (or hyperprofileration) of skin cells leading to scaly patches or plaques. The plaques can often be dry and inflamed. There are five main types but the most common is plaque psoriasis (*psoriasis vulgaris*). There are three levels of severity (mild, moderate and severe) which are measured according to the percentage of the surface area of the skin affected. Mild is <3%, moderate is 3-10% and severe is >10%. The majority (80%) of patients have mild psoriasis.

22. There is no cure for psoriasis and treatments are used to alleviate symptoms. Even when symptoms disappear, relapses are common. Thus treatments may need to be long term in nature. Sometimes different treatment options are alternated so that an initially more potent treatment is used as a clearing phase while longer term treatment to maintain such clearance and/or alleviate symptoms is used as a maintenance phase.

23. Traditionally local treatments include topical medicines and photo-treatment. Systemic treatments have also been used (such as methotrexate, retinoids, cyclosporine or acitretin). These were reserved for more severe psoriasis.

24. Topical treatments were the most common first line approach and two of the main ones were vitamin D analogues (such as calcipotriol) and corticosteroids (such as betamethasone). Other topical treatments were dithranol and coal tar.

25. Topical treatments included solutions (or lotions), creams and ointments. Each had their own advantages and disadvantages. Lotions were liked by patients as they were thinner with a fast absorbing disappearing effect. Ointments were heavier and greasy and not always liked by patients. Creams were somewhere between the two. However despite the differences between these kinds of topical treatment, all three were widely used and accepted forms.

26. Patient compliance was an important factor. Although in severe cases a patient would be likely to comply with the treatment in order to alleviate their symptoms, in the majority of cases where the psoriasis was mild and reasonably contained there would be a greater risk that a patient might not comply with the treatment if it was disruptive of their daily routine, unpleasant to apply, had adverse local side effects (e.g. irritation) or more serious side effects (e.g. skin atrophy or systemic effects).

27. By 1999 corticosteroids were a well established treatment for psoriasis. However there were serious problems with their long term use, particularly of the more potent kinds of corticosteroids. The side effects of corticosteroids included tachyphylaxis (acute tolerance), skin atrophy, adrenal gland suppression and rebound (whereby after withdrawal from corticosteroid treatment the psoriasis came back, possibly in an exacerbated form). For these reasons corticosteroids were frequently used only as short term treatments.

28. Betamethasone was a potent topical corticosteroid, although it was not the most potent kind available. It could take the form of either the valerate or dipropionate ester. The properties of these two different forms were not identical but for the purposes in this case betamethasone can be regarded as a single agent.

29. In the 1990s the vitamin D analogue calcipotriol had been introduced successfully by LEO. It revolutionised topical treatment for psoriasis. It was effective but did not suffer the long term side effects of corticosteroids. By 1999 calcipotriol was a well established treatment. One drawback was that its use was associated with a degree of skin irritation.

30. By 1999 clinicians were co-prescribing a number of different combinations of agents to treat psoriasis. A commonly used combination was to prescribe calcipotriol and a topical corticosteroid such as betamethasone. This made sense because the two agents have different modes of action and different side effect profiles. The combination of calcipotriol and a corticosteroid was well established at the priority date. A particular reason, in addition to the expected advantage in terms of efficacy of using the two drugs together, was that the corticosteroid might also address the irritation which could be caused by calcipotriol.

31. These combined treatments involved prescribing the two agents separately and involved the patient applying them separately. For example one approach was to apply a corticosteroid cream in the morning as it was easy to apply and less likely to mark clothing and apply a vitamin D analogue ointment in the evening as it would moisturise and occlude the skin while the irritation would be less important since the patient would be asleep. Other treatment regimens for the co-prescribed products were used as well.

32. The skilled clinician would also know that there were some formulation products in which two agents were combined together which were used in dermatology in 1999. A drawback of combining two drugs in a single formulation is that the relative doses of the two agents are fixed, reducing the ability to tailor the treatment to an individual patient. On the other hand they provide a benefit in that they can be more convenient to apply than two products separately. The skilled clinician understood both these advantages and disadvantages. The skilled clinician knew that a single fixed combination formulation of two drugs would be likely to improve patient compliance since only one product needs to applied instead of two different ones.

33. LEO submitted that the skilled clinician knew that a co-formulation of calcipotriol and a corticosteroid was not possible or at least difficult because the two agents required a different pH to be stable and so a formulation in which one was stable would degrade the other one. However I am not satisfied it was part of the common general knowledge of the skilled clinician for two reasons. First it related to

formulation, with which most clinicians were not concerned. Second, while it is clear that Professor van der Kerkhof believed that to be the case and that this view is supported by documents cited by LEO in this case, I am not satisfied it is a view held sufficiently widely to reach the standard for common general knowledge. Professor Gawkrodger was not aware of it.

34. I turn to consider the skilled formulator.

35. A topical formulation is one applied to body surfaces, mainly the skin. Common topical formulations are lotions, ointments, creams and gels. A lotion is a liquid containing the therapeutic agent usually in solution. An ointment is a semi solid in which the major component is an oil based phase (such as soft white paraffin like Vaseline). A cream is a mixture of two immiscible liquids (e.g. oil and water). Examples are oil-in-water and water-in-oil emulsions. A gel is a gelatinous semisolid which can have thixotropic properties.

36. Excipients are substances present in a formulation other than the therapeutic agent. They can perform numerous functions. Solvents dissolve the agent. An emollient gives the quality of softening or soothing the skin. An emulsifier stabilises an emulsion. A penetration enhancer decreases the barrier resistance of the outmost layer of the epidermis and allows the agent to penetrate more readily into the skin. There are many other functions which excipients can perform.

37. Solubility plays a key role in formulation development as the target dose and concentration of the agent are critical target parameters. Solvents are selected in pre-formulation studies. Formulators have mental "go to" lists of excipients. The decision about what solvents to test is taken based on the skill and knowledge of the formulator. The inclusion of a new excipient in a formulation would require similar testing as for a new drug.

38. The pH of an aqueous solution is a measure of the concentration of hydrogen ions. Solutions with a pH less than 7 are acidic whereas above 7 they are alkaline. The stability and solubility of a drug can be affected by pH. Therefore in pre-formulation compatibility studies it is important to evaluate drug solubility and stability over a wide pH range (typically 3 – 10). Buffers for pH may be used. Even in systems in which water is not added as an excipient, there may be water present and so pH may remain an issue. Professor Brown referred to "apparent pH" and explained it was a standard term used to describe pH of a partially aqueous composition. Professor Crowley had not heard the term. I accept Professor Brown's evidence on this point.

39. The concept of apparent pH reflects the fact that skilled formulators knew that even if a non-aqueous system was chosen (such as a paraffin based ointment) in practice it was unlikely to be possible to remove all the water from a system. Even if a lab based formulation was truly dry, some water was likely to be encountered during manufacture, processing and in the product's lifetime. Thus I do not accept Professor Crowley's view that by choosing to use an ointment a skilled formulator would simply put to one side any concerns about pH dependent stability. Such considerations would always play a part.

40. However in the end the skilled formulator is an empiricist. Exactly how these various considerations will play out in practice is hard to predict in advance and always

requires testing. For example that is why pre-formulation compatibility studies are always carried out.

41. Considering calcipotriol from the point of view of the skilled formulator, the position was this. Such a person called on to play a part in the relevant team may not have made a calcipotriol product before, however this makes no practical difference. LEO's submissions characterised calcipotriol as a "delicate" molecule. That is a reference to the fact that in terms of pH it required an alkaline pH to be stable and was liable to degrade at more acidic pH. A skilled formulator who had worked on calcipotriol would know about this pH stability profile as part of their common general knowledge. A skilled formulator who had not worked on calcipotriol before would find out these facts very early in the process of developing a formulation either from literature or from pre-formulation studies.

42. Considering betamethasone, the skilled formulator was more likely to have had direct experience of formulating corticosteroids than calcipotriol but in any event again it makes no difference. Their common general knowledge, one way or another, would include the fact that these agents were formulated at an acidic pH to optimise stability.

The patent

43. The 808 patent explains that the invention concerns pharmaceutical compositions for dermal use which contain at least one vitamin D analogue and at least one corticosteroid. It points out that these two classes of agent have a low compatibility with respect to the pH values for stability. The patent acknowledges that it is common to use both agents in combination to treat psoriasis, albeit they are formulated separately and states that until now a topical composition comprising the combination of both agents together has not been described. There is an acknowledgement that patient compliance using a two component regimen was a problem.

44. The object of the invention is to provide a composition for dermal use for the treatment of psoriasis in which both agents are together. The solution presented by the patent is a formulation within the claims. It is a "non-aqueous" formulation, which means that water has not been added to it. The core idea in the patent is a formulation consisting of a vitamin D analogue such as calcipotriol, a corticosteroid such as betamethasone (as dipropionate) and a solvent from a specified class. The Examples use a solvent described as Arlamol E (polyoxypropylene-15-stearyl ether). The patent gives the results of stability tests which show that the tested formulation is very stable under the test conditions.

45. The patent also reports the results of clinical studies. In the tests the combination product is tested against each component given alone. TEVA criticised the tests to some extent but it is clear that they are on a substantial scale and show that the combination product gives better results than either monotherapy. One characteristic which can be seen is that the onset of effectiveness is faster with the combination than either component alone.

46. The patent states that the results demonstrate synergy. In some patent cases there is a major dispute about the nature of synergy and whether results are truly synergistic. That debate did not arise in this case and I do not have to address it. These results

clearly show that the combined formulation is an effective treatment for psoriasis. That is undisputed.

Claim construction

47. Attached as Annex 1 and 2 are the proposed amended claims of the 808 and 083 patents as sought by LEO. Within those sets of claims, LEO contended that claims 1, 2, 4, 5, 6, 7, 8, 10 and 11 of the 808 patent as proposed to be amended and claims 1, 2, 3, 4, 5, 6, and 7 of the 083 patent as proposed to be amended were all independently valid.

48. Two minor points arose in relation to the language used in claim 1. In claim 1 of 808 the word "and" is used in the list of diseases to be treated (psoriasis, sebopsoriasis and seborrhoic dermatitis) whereas in claim 1 of 083 the word is "or". LEO submitted that in context both claims meant the same thing in this respect, that the list of diseases is disjunctive. I accept that. Professor van der Kerkhof's view was that it was plausible given the results for psoriasis that the invention would be suitable for the other two diseases. They did not play a major part in this case.

49. Claim 1 of 808 refers to "optimum stability pH" and "optimum pH". LEO submitted these two meant the same thing. TEVA did not dissent and I accept LEO's submission. This issue played no part in the trial.

Obviousness

50. The structured approach to the assessment of obviousness was set out by the Court of Appeal ***Pozzoli v BDMO*** [2007] EWCA Civ 588, [2007] FSR 37. It is:

> (1) (a) Identify the notional person skilled in the art;
>
> (b) Identify the relevant common general knowledge of that person;
>
> (2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
>
> (3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;
>
> (4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?

51. In ***Medimmune v Novartis*** [2012] EWCA Civ 1234 the Court of Appeal emphasised that the nature of the court's task was ultimately to answer a single question of fact (see e.g. Kitchin LJ paragraph 93 and Lewison LJ paragraphs 177 to 186).

52. In ***Conor v Angiotech*** [2008] UKHL 49, [2008] RPC 28 the House of Lords considered the issue of obviousness. There Lord Hoffmann (with whom the others of

their Lordships agreed) approved the following statement of Kitchin J made in ***Generics v Lundbeck*** [2007] RPC 32:

> "The question of obviousness must be considered on the facts of each case. The court must consider the weight to be attached to any particular factor in the light of all the relevant circumstances. These may include such matters as the motive to find a solution to the problem the patent addresses, the number and extent of the possible avenues of research, the effort involved in pursuing them and the expectation of success."

53. LEO emphasised two judgments of Floyd J (as he then was) which considered the role of "obvious to try" in the assessment of inventive step. They were ***LEO Pharma v Sandoz*** [2009] EWHC 996 (Pat) and ***Omnipharm v Merial*** [2011] EWHC 3393. These judgments show that "obvious to try" is simply one of a variety of factors which fall to be considered. The significance of these factors varies from case to case and depends on the facts. Obvious to try cases usually involve consideration of the level of expectation of success but one cannot lay down a general characterisation of what the true level of expectation must be in every case beyond stating that it must be a fair one. In that way the differences between different cases is taken into account. It is wrong to ask whether something might achieve a particular desired effect. It is correct to ask whether it was obvious that it would achieve that effect.

Skilled person and the common general knowledge

54. I have identified the skilled person and the common general knowledge above.

Inventive concept

55. Despite the 16 claims said to be independently valid, in fact the obviousness case turns on a single claim. TEVA contend that it was obvious to use polyoxypropylene-15-stearyl ether (Arlamol E) as a solvent for a non-aqueous calcipotriol / betamethasone fixed combination ointment formulation for dermal use to treat psoriasis. The betamethasone could be in the form of the valerate or dipropionate ester (both are said to be obvious).

56. Such a formulation would fall within all of the 16 claims said to be independently valid in both patents. I can therefore take the relevant inventive concept to be a non-aqueous ointment formulation for dermal use to treat psoriasis comprising calcipotriol, betamethasone and polyoxypropylene-15-stearyl ether as a solvent. In this obviousness section of the judgment I will refer simply to betamethasone as the corticosteroid of interest and I will not distinguish between that agent or its valerate or dipropionate esters. There is no need to do so.

Identify differences

57. Most obviousness attacks involve a primary documentary reference. The differences between the primary reference and the invention can be identified (***Pozzoli***). Some other source, such as the common general knowledge or a secondary reference which it was obvious to find, may provide the solution to a problem arising from the primary reference. There is no need to establish whether the primary reference would be

found by a skilled person or was part of the common general knowledge because as a matter of principle the invention must be inventive over everything in the state of the art and so the skilled person is deemed to read the primary reference properly and with interest (e.g. ***Ratiopharm v Alza*** [2009] EWHC 213 (Pat)).

58. Some attacks are based on common general knowledge alone, in which case all the elements of the invention are said to derive from common general knowledge alone and no distinct issue arises as to whether the skilled person would find a piece of information.

59. TEVA's case starts from the proposition that there was an obvious desire to develop a fixed combination product of calcipotriol and betamethasone. This is said to derive from the common general knowledge. The skilled person considering this problem is then presented with Turi, which is said to render the invention obvious in that context because it provides the third element of the claimed combination, the solvent, Arlamol E. So TEVA's case is unusual in that it starts from common general knowledge and then involves adding information from a document (Turi) which is not part of the common general knowledge and which TEVA do not submit would be found on a literature search. TEVA rely on the principle that any document forming part of the state of the art must be placed before the skilled person. Turi on its own does not lead a skilled person to the invention in this case. Although LEO contend that the argument fails on the facts, they did not object to the argument in principle. I will return to this below. At this stage it means that there is no point in identifying the differences between the invention and a primary reference.

Is the invention obvious?

60. TEVA's argument starts with the proposition that a combination product was a logical alternative to the well known treatment regimen at the priority date. These included a regimen in which a corticosteroid such as betamethasone and a vitamin D analogue such as calcipotriol were formulated separately and applied at different times. LEO did not agree. They contended that a fixed combination product was not obvious.

61. By 1999 the use of two agents was well established in the treatment of psoriasis. Many patients were prescribed a combination of topical calcipotriol and a topical corticosteroid. To the skilled clinician at the time (1999) a single formulation combining betamethasone and calcipotriol for dermal use to treat psoriasis was a desirable thing because it would help patient compliance and convenience. It was obvious that a patient given a single product to apply would be more likely to apply it correctly over time than a patient given two different products and told to apply them at different times. It was widely recognised that many patients failed to apply their prescribed topical treatments correctly.

62. It is true, as Professor van der Kerkhof's evidence emphasised, that the sort of carefully tailored treatment regimes which highly professional specialised consultant dermatologists would prescribe would be less likely to use a fixed dose combination product but I accept Professor Gawkrodger's evidence that for other doctors a fixed dose combination product would be useful. Such a product was not for every patient but there were patients for whom a fixed combination would be very good because it would encourage compliance. That advantage of a fixed combination is entirely obvious.

63. I will now consider what the expectations of the skilled clinician would be about the clinical efficacy of a co-formulation. First, it was obvious that a combined regime using both calcipotriol and a corticosteroid was more efficacious than monotherapy, after all that was the reason why doctors prescribed the two treatments together. Second, I bear in mind in particular Professor van der Kerkhof's evidence about the *Papp* paper in cross-examination and his evidence in re-examination. Taking his evidence as a whole, his opinion was that a skilled clinician would expect that, on the assumption that a suitable stable formulation of these two agents could be produced (which he understood not to be the case), the clinical efficacy of the co-formulation would be likely to be better than either agent alone, however the clinician would never assume that that was so and would always require clinical tests to be performed. In my judgment it was reasonable for a skilled clinician in 1999 to expect a suitable combined product (if made) to have positive clinical results. It was also well known that the use of a corticosteroid could reduce the slight irritation associated with calcipotriol.

64. TEVA submitted that it was obvious that a fixed combination would address certain particular problems with the side effects of calcipotriol and corticosteroids when administered separately. I do not accept that. Such a combination might have done so but it was not obvious it would do so.

65. LEO contended there was a prejudice against the use of corticosteroids and so it would not be obvious to make any combination product including them. They relied on Professor van der Kerkhof's evidence in which he explained clearly that by 1999 it was well understood that there were severe potential side effects associated with corticosteroid use. I accept that evidence. They were inappropriate for long term, chronic use. Nevertheless it is also the case that corticosteroids were in 1999 a very well established treatment for psoriasis. They were probably the most commonly used agents for the treatment of mild to moderate psoriasis worldwide. I reject the submission that there was a relevant prejudice against their use in the short term or clearing phase of treatment at any level of the medical profession (from "top end" consultants to general practitioners). There was no prejudice which would make it inventive to consider a corticosteroid as a component in a fixed dose combination with calcipotriol. In the end I do not think Professor van der Kerkhof really supported the view that there was a prejudice against the use of corticosteroids but if he did maintain that view then I was not convinced.

66. There was no express reference to the idea of a fixed combination of a corticosteroid and calcipotriol in any of the prior art literature and LEO relied on this as an indication that such a fixed combination was not obvious. TEVA answered this by pointing out that calcipotriol was for all that time a patented product protected by LEO's patent rights which reduces the force of that point somewhat. No other pharmaceutical company would be interested in supporting or considering a development of that kind in those circumstances. There is some force in TEVA's argument but it is not a complete answer to the point. It is notable that apart from Professor Gawkrodger himself, who gave clear evidence that he had thought of it, none of the literature proposes a fixed combination before 1999.

67. Another likely factor explaining in part why a combined corticosteroid - calcipotriol formulation is not discussed in the literature before 1999 was because there was a belief amongst many clinicians that the two drugs were or might be incompatible

from a formulation point of view due to their differing pH stability profiles (see e.g. the Kragballe paper on Vitamin D3 Analogues published in 1995). The point may explain in part why the literature does not discuss combined corticosteroid – calcipotriol formulations but the argument cannot be taken too far. The phenomenon was not a clinical issue, it was a question for a formulator. I have already found that the pH incompatibility of calcipotriol or corticosteroids was not part of the common general knowledge of the skilled clinician in 1999.

68. In my judgment, bearing in mind all the points discussed so far, to a skilled clinician in 1999 the idea of a fixed dose combination of calcipotriol and a corticosteroid such as betamethasone was an obvious one.

69. At this stage it is convenient to address the motivation of the skilled clinician concerning a combined calcipotriol - betamethasone formulation. First and importantly they would expect it to improve patient compliance as compared to giving the two drugs separately. That alone was a sufficient motivation to take a project like this forward since compliance problems with the two drugs prescribed separately was part of the common general knowledge. Second, I have found that the skilled clinician would expect that, assuming a fixed dose formulation could be made which was stable (and in which the agents were bioavailable), then it would be an effective treatment for psoriasis, better than monotherapy. After all the skilled clinician was already familiar with the advantages of co-prescribing the two agents separately. How effective the treatment would in fact turn out to be from a clinical standpoint would always have to be tested but the expectation of clinical success would be quite sufficient to motivate the skilled team to go ahead and try to produce a viable formulation. In other words it was obvious to the skilled clinician member of the skilled team that the team should set about making a combination of calcipotriol and betamethasone for the topical treatment of psoriasis. I turn to examine the invention from the perspective of the skilled formulator.

70. To a skilled formulator in 1999 one obvious thing to do was to use the simplest topical formulations possible. An ointment was one of the simplest formulations. An important advantage of ointments for a formulator considering a combination of calcipotriol and corticosteroids in general (or betamethasone in particular) relates to the pH incompatibility issue. The skilled formulator would be aware of the incompatibility of the pH stability profiles of the two agents as a matter of his or her common general knowledge. However a way forward to address this problem would also be a matter of common general knowledge. That would be to aim for a non-aqueous ointment formulation. Using an ointment allows the formulator to produce a non-aqueous formulation unlike for example a cream, which consists of an oily phase and a water-based phase. The skilled formulator could not be sure that a non-aqueous ointment formulation would work but it would be well worth investigating thoroughly since, by having an oil based system with no added water, the risk of problems based on pH or apparent pH would be minimised. The risks would not be eliminated but I am quite sure a skilled formulator would not stop at this stage. They would have a sufficient motivation to think a solution was possible for a non-aqueous ointment to be worth trying.

71. A simple ointment consists of the active ingredient(s), a base such as white soft paraffin and a solvent. Since white soft paraffin was used as the base both for

calcipotriol and for betamethasone ointments at the priority date, it would be entirely obvious to use that as the base for the putative formulation combining the two.

72. The real issue at this stage is about the solvent. The skilled formulator would carry out compatibility tests on a number of possible solvents. The number would be about 10 to 20. This sort of screening was entirely routine. The solvents included in these screening tests would be selected by the skilled formulator based on their knowledge and experience. The formulator would bring their experience to bear and consider the characteristics of the agents and the conditions in which they were to be used in choosing what solvents to test.

73. Arlamol E (polyoxypropylene-15-stearyl ether) was not a compound which the skilled formulator would be aware of as part of their common general knowledge. However it is discussed in Turi and it is at this stage that TEVA contends the skilled team are to consider the Turi document.

The disclosure of Turi

74. Turi is a US patent belonging to the pharmaceutical company Upjohn published in 1978, 20 years before the priority date of the LEO patents. It relates to topical preparations containing anti-inflammatory steroids. Turi describes polyoxypropylene-15-stearyl ether as a product which is already marketed under the trade mark Arlamol E by ICI as an emollient solvent for cosmetic products. It states that the compound has not been disclosed before for use as a solvent in pharmaceutical preparations with anti-inflammatory steroids for topical administration. The invention disclosed in Turi is the idea of using the compound in that way. Turi states that these topical formulations have advantages (non-irritating, having lubricant properties, being antibacterial and anti-fungal). The advantages relating to irritation and lubrication are presented as being improvements over the use of the known good solvent propylene glycol.

75. Turi describes the compound in detail (at col 3 ln65 – col 4 ln35) and refers to an ICI datasheet. There are ten example formulations which use the compound. Example 4 describes a betamethasone valerate ointment which uses the compound. No water is added to that formulation.

76. LEO described the benefits ascribed to the compound by Turi as illusory. That is an overstatement. The position is as follows. No stability data are presented in Turi. Moreover what is said about the relative advantages of polyoxypropylene-15-stearyl ether as opposed to propylene glycol would not be regarded as significant by a skilled formulator in 1999. I accept Professor Brown's evidence that irritancy was not in 1999 a major concern with propylene glycol. Any advantage relating to emolliency as compared to propylene glycol was not significant since, to the extent the formulator wished to address emolliency, it could be provided by other excipients. The existence of anti-fungal and antibacterial properties of polyoxypropylene-15-stearyl ether would not be regarded as significant.

77. Nevertheless a skilled formulator who read Turi as a whole in 1999 would not then ignore it or dismiss it. It discloses the idea of using polyoxypropylene-15-stearyl ether as a solvent in a topical non-aqueous formulation of a corticosteroid such as betamethasone.

What would the skilled formulator do having read Turi?

78. TEVA submitted that a skilled formulator given Turi would include polyoxypropylene-15-stearyl ether in the routine screening tests mentioned above. LEO did not agree. The debate depends on how the skilled formulator would approach the question of selecting solvents to test.

79. The skilled formulator would decide what compounds to test based on the properties of the compounds. LEO emphasised Professor Brown's evidence that familiarity with such compounds would be a critical element in the skilled formulator's thinking. I accept that familiarity would always play a part in the choices made by real formulators working in real organisations since it maximises the chances of success by using tried and tested compounds which are often found to work. However I find that the notional skilled formulator would not be as conservative in his or her thinking as that evidence might suggest. The well known and frequently used excipients, such as propylene glycol, are such because they are often found to work well in topical formulations. The outcome of the tests would not be known in advance (otherwise there is no point in doing the test). The notional skilled formulator would test some familiar compounds but, subject to the regulatory point considered below, would not be put off from including unfamiliar compounds merely because of their unfamiliarity. The question is primarily a technical one and would be decided based on consideration of the known properties and desired characteristics of the compound.

80. The skilled formulator would have no reason to doubt the essential idea disclosed in Turi, that the compound, which was one they had never heard of before, could be used as a solvent in a topical steroid formulation. The fact that unlike many other possible solvents, this compound did not have a well established track record in pharmaceutical formulation, would not be sufficient to put the formulator off including it in the test.

81. LEO raised regulatory considerations as a reason why it would not be obvious to use polyoxypropylene-15-stearyl ether. There was evidence that the compound had been used in one approved pharmaceutical product (not betamethasone) but it was plainly not a widely used pharmaceutical excipient. The argument is that because the skilled formulator would know that the compound has not been used widely in pharmaceutical formulations before, the skilled formulator would be discouraged from using it since that would add potential cost, time and uncertainty to the process. The relevant pharmaceutical regulator might well require extensive testing before granting marketing approval. In support of this LEO referred to issues relating to the compound which arose during the process of seeking approval from one regulator for the product of the invention.

82. LEO cited the judgments of Lewison J (as he then was) in ***Ivax Pharmaceuticals v Akzo*** [2006] EWHC 1089 (Ch) (paragraphs 46-47) and Arnold J in ***Mylan v Glaxo Wellcome*** [2013] EWHC 148 (Pat) at paragraph 110 for the proposition that commercial considerations are factors which may play a role in the thinking of the person skilled in the art. The way it was put by Lewison J was that it cannot be said they are completely irrelevant. In my judgment commercial considerations, such as the uncertainties surrounding the regulatory process relating to an invention in the pharmaceutical field, are capable of playing a role in the thinking of the notional skilled person as a matter of principle. However, first, like any other factor their

significance will vary from case to case; and second given that they are commercial rather than directly technical in nature, these factors are unlikely to outweigh technical consideration in any but the strongest cases.

83. The key factors which have a bearing on the significance of regulatory considerations in this case are these. First the compound would be one unfamiliar to the skilled formulator. They would not themselves have used it before nor would they have known before of its use in a product which obtained regulatory approval. However, second, the information from Turi and the ICI data sheet would be encouraging. There is no ostensible reason why it might fail to obtain approval. Third, although it was not widely used, the compound is listed in one important source, the FDA's Inactive Ingredient Guide. A skilled formulator considering the compound having read Turi would find this reference. This is important because it means the compound has been approved for use by a regulator. In any real project regulatory considerations will always play a part but in my judgment in this case the regulatory factors are not sufficiently strong to have any material bearing on the decisions made by the skilled formulator.

84. I turn to consider the properties of polyoxypropylene-15-stearyl ether from the point of view of a skilled formulator thinking whether to include it in routine tests. The compound appears to be useful as a solvent suitable for topical use in non-aqueous ointments with corticosteroids in general and betamethasone in particular. These are important points in its favour. It is reported as having a water content of 0.7% (Turi col 4 ln33). LEO submitted that this was a higher water content than propylene glycol (0.2%). True but I find that difference would not be regarded as significant. Professor Brown's evidence in cross-examination was that as long as the water content was less than about 2%, water content would not lead to a putative compound being taken off his "go to" list (in other words his list of compounds to test).

85. There is no evidence about its utility with calcipotriol, however that would not put off the skilled formulator from including it. At the relevant date calcipotriol was only available in one (or a very few) approved formulations. Thus inevitably the skilled formulator is going to test excipients which have never been used with the compound before. Another factor which would not put off the skilled formulator is the fact it may have a minor odour.

86. There was some suggestion that an analogy might be drawn between the compound and another class of excipients known as the Brij series. I reject that. The analogy was not meaningful.

87. In cross-examination Mr Alexander put a table to Professor Brown which sought to summarise the properties of various excipients, including polyoxypropylene-15-stearyl ether. The table was an exercise in advocacy designed to enhance the appearance of similarities between the compound and some well known excipients. It ignored several inconvenient facts as far as TEVA are concerned. I will mention two. First the fact that the other excipients are not just present in references such as the IIG but are well established on the market. Second the fact that the properties of the other excipients are well established whereas the table treats the claims made in Turi for the properties of the compound as similarly well established facts. I will not place weight on the table.

88. The overall question of whether a skilled formulator given Turi would include polyoxypropylene-15-stearyl ether in the routine screening tests is a multifactorial one. In summary, Professor Crowley's view was that it was obvious to use the compound whereas Professor Brown's view was that is was not. However detailed elements supporting each expert's overall view were undermined in cross-examination.

89. Mr Carr put to Professor Crowley that LEO themselves experienced difficulties in formulating the combination using propylene glycol in a non-aqueous ointment. Professor Crowley accepted that propylene glycol did not work. LEO pointed out to Professor Crowley that TEVA themselves have a patent application (WO 2008/027532), later than the LEO patent in this case, addressed to the very same problem of the incompatible pH stability of corticosteroids and vitamin D analogues (such as calcipotriol) in a topical formulation. It claims the use of certain other compounds as solvents such as triglycerides and polysorbate. Professor Crowley accepted that this showed that the incompatible pH stability problem of these two ingredients "would be a real problem and would require a lot of work to solve it". This is important evidence in LEO's favour.

90. Professor Brown's evidence did not remain untouched by the cross-examination either. His clear view expressed in his reports was that the formulator would not include the compound in a solvent screen. The cross-examination showed that the Professor's key reason for not including it was that he had not heard of it. The cross-examination showed that based on its ostensible properties, it was a suitable candidate for testing. The skilled formulator would have no personal experience with the compound but there was no reason to doubt that it was a suitable candidate to test.

91. LEO submitted that the difference between the views of the two formulator experts reflected the relative state of their experience in topical formulations. Professor Crowley's view was that the fixed combination would have been simple and have had a high prospect of success and Professor Brown's view was that it would have been difficult and had a low prospect of success. LEO submitted this could be explained simply by Professor Brown's greater experience as a real specialist in topical formulations. I agree the relative experience of the two witnesses is a relevant factor but it is not a factor of overwhelming weight in this case because the outcome turns on the detailed issues which fall to be considered, not the overall opinions of the experts.

92. Stepping back and considering the evidence as a whole, there are undoubtedly points in LEO's favour on this issue but despite them I found TEVA's case more persuasive. A skilled formulator considering what solvents to test and presented with Turi would have no reason to disregard its teaching that polyoxypropylene-15-stearyl ether could be used as a solvent in topical preparations of corticosteroids. They would have no reason to doubt that it would in fact work in that way, as taught by Turi. That would be sufficient grounds to include the compound in pre-formulation tests. Based on what the skilled formulator knew about it at the time there was a sufficient prospect of a positive result in the tests with this compound to make it worth testing. It was obvious to do so.

Next steps

93. The results of the tests on polyoxypropylene-15-stearyl ether would be positive. The skilled formulator would take forward a non-aqueous ointment using the compound as a solvent.

94. At this stage I should mention the possibility of inventive selections. There is evidence that LEO had problems trying to make a non-aqueous combination formulation using propylene glycol as the solvent. Although that evidence is not as robust as it could be, I accept it. However I am not satisfied about the position of other solvents. No skilled formulator would test only propylene glycol. Professor Brown described a number of other solvents on his "go to" list and all or many of them would also be tested. There is no proper evidence either way as to whether they work or not. In some cases there is evidence from the inventors to show that they tested a vast range of apparently obvious agents but that none worked. The claimed compound may be the only one found to work after many failures. Such an argument in this case might have been supported by the TEVA patent application. When properly established in evidence this sort of factor can be compelling evidence of non-obviousness. There is not sufficient evidence here to draw such an inference.

95. Accordingly it cannot be said that the stability of a non-aqueous ointment formulation of the two drugs and polyoxypropylene-15-stearyl ether represents a selection of a working solvent from a wider class which did not work. Equally to a skilled team given Turi, the fact the compound actually works cannot be characterised as surprising.

96. Having got this far, there is no reason to doubt that the skilled formulator would succeed in producing an ointment formulation consisting of betamethasone, calcipotriol and the compound. Whatever pH incompatibility exists between these two agents in other contexts, this formulation would be stable. There was no evidence in this case that there would be any undue concern about bioavailability since Professor van der Kerkhof said in re-examination that assuming the formulation is stable, the agents within would be expected to have good bioavailability.

97. As I have already said, the skilled team would expect a stable, bioavailable formulation to provide a compliance benefit and to be an effective treatment for psoriasis, better than monotherapy. They would be motivated to carry out a clinical study to confirm that expectation. The study would show that formulation was an effective treatment.

98. Accordingly all the claims of both patents are obvious.

Reflections on TEVA's obviousness case in principle

99. I have considered whether TEVA's obviousness case is an example of the unfair step by step approach identified in ***Technograph***. I do not believe it is. The steps considered above are the normal steps in the development of a pharmaceutical product like the one in issue. It is not an exercise in hindsight to consider them in this way.

100. I have also paused to consider whether LEO's position is right in accepting that the court must consider the impact of Turi on the thinking of the skilled team at the stage in the argument it arises. TEVA's argument only works if Turi is notionally presented to the skilled person at a specific point in the sequence of steps. An

inevitable element of this approach is that it does not matter what the skilled clinicians might have thought of Turi. It is not a document addressed to them.

101. In my judgment LEO were right not to object in the particular circumstances of this case but it does not follow that it will always be legitimate to consider obviousness in this way. The key element here is that the common general knowledge alone would lead the skilled person to think of the combination, would motivate the skilled person to combine the two active agents in a non-aqueous ointment formulation and would motivate the skilled person to draw up a list of solvents to test for use in the ointment. All the steps up to the point of considering Turi derive from the common general knowledge alone.

Insufficiency

102. TEVA's insufficiency argument was advanced as a fall back in the event the patents were found to be inventive. It does not arise on my findings above.

Added matter

103. TEVA submitted that all the claims currently sought by LEO were bad for added matter. It was an independent ground of invalidity however I do not propose to deal with it because it does not depend on any court (at this level or on appeal) making findings of fact by resolving disputed evidence. It is primarily a matter of construction and is therefore something an appellate court would be able to resolve if necessary.

Infringement

104. The product described in TEVA's confidential product and process description would plainly infringe the claims I have considered above if those claims were valid. There was no argument to the contrary.

Conclusion

105. I find both LEO patents are invalid for lack of inventive step.

Annex 1

Proposed claims of 808 patent

1. A non-aqueous pharmaceutical composition for dermal use to treat psoriasis sebopsoriasis and seborrhoic dermatitis in humans and other mammals, said composition comprising a first pharmacologically active component A consisting of at least one vitamin D or vitamin D analogue and a second pharmacologically active component B consisting of at least one corticosteroid wherein the difference between the optimum stability pH of said first component A and the optimum pH of said second component B is at least 1; and further comprising at least one solvent component C wherein said first component A is selected from the group consisting of calcipotriol, calcitriol, tacalcitol, maxacalcitol, and 1(S),3(R)-dihydroxy-20(R)-[(3-(2-hydroxy-2-propyl)-phenyl)-methoxy)-methyl]-9,10-seco-pregna-5(Z),7(E),10 (19)-triene, as well as mixtures thereof and wherein said second component B is selected from the group consisting of Betamethasone, Clobetasol, Clobetasone, Desoximethasone, Diflucortolon, Diflorasone, Fluocinonid, Flumethasone, Fluocinolon, Fluticasone, Fluprednidene, Halcinonide, Hydrocortisone, Momethasone, Triamcinolon, and pharmaceutically acceptable esters and acetonides as well as mixtures thereof, and wherein said component C is selected from compounds of the general formula $H(OCH_2C(R^1)H)_xOR^2$ (II) and mixtures thereof, wherein x is in the range of 2-60, R^1 in each of the x units is CH_3, and R^2 is straight chain or branched C_{1-20} alkyl or benzoyl.

2. A composition for use according to the preceding claim wherein said vitamin D analogue is calcipotriol.

3. A pharmaceutical composition for use according to any of the preceding claims wherein said esters or acetonides are selected from the group consisting of 17-valerate, 17-propionate, 17,21-dipropionate, acetonide, acetonide-21-N-benzoyl-2-methyl-β-alaninate, acetonide-21-(3,3-dimethylbutyrate), and 17-butyrate.

4. A pharmaceutical composition for use according to claim 1 wherein the corticosteroid is betamethasone or an ester, such as the 17-valerate or 17,21-dipropionate.

5. A pharmaceutical composition for use according to any of the preceding claims wherein said component C is selected from compounds of the general formula $H(OCH_2C(R^1)H)_xOR^2$ (II) where R^1 and R^2 are as defined in claim 1 and x is in the range of 10-20, and mixtures thereof.

6. A pharmaceutical composition for use according to any of the preceding claims wherein said component C is polyoxypropylene-15-stearyl ether.

7. A pharmaceutical composition for use according to any of the preceding claims wherein said vitamin D analogue is calcipotriol and wherein the corticosteroid is betamethasone or an ester, such as the 17-valerate or 17,21-dipropionate.

8. A pharmaceutical composition for use according to claim 7 wherein the corticosteroid is betamethasone 17,21-dipropionate.

9. A pharmaceutical composition for use according to any one of the preceding claims containing 0.0001 to 0.025% w/w of said component A and 0.005 to 0.1% w/w of said component B and 1 to 20% w/w of said solvent component C.

10. A pharmaceutical composition for use according to any preceding claim, in the form of a monophase composition.

11. A pharmaceutical composition for use according to the preceding claim, which is an ointment.

12. A pharmaceutical composition for use according to any preceding claim, wherein in the treatment, the composition is applied topically once or twice daily in a medically sufficient dosage.

Annex 2

Proposed claims of 083 patent

1. A non-aqueous topical pharmaceutical composition in the form of an ointment, a cream, a lotion, a liniment or other spreadable liquid or semi-liquid preparation for dermal use in the treatment of psoriasis, sebopsoriasis or seborrhoic dermatitis in humans and other mammals, said composition comprising a first pharmacologically active component A consisting of calcipotriol and a second pharmacologically active component B consisting of betamethasone or an ester thereof and further comprising at least one solvent component C wherein said component C is selected from compounds of the general formula $H(OCH_2C(R^1)H)_xOR^2$ (II) and mixtures thereof, wherein x is in the range of 2-60, R^1 in each of the x units is CH_3, and R^2 is straight chain or branched C_{1-20} alkyl or benzoyl.

2. A pharmaceutical composition for use according to claim 1, wherein component B consists of a betamethasone ester, such as the 17-valerate or 17,21-dipropionate.

3. A pharmaceutical composition for use according to any one of the preceding claims wherein component B is betamethasone 17,21-dipropionate.

4. A pharmaceutical composition for use according to any one of the preceding claims in the form of a mono-phase composition.

5. A pharmaceutical composition for use according to the preceding claims which is an ointment.

6. A composition for use according to any of the preceding claims, wherein said component C is selected from compounds of the general formula $H(OCH_2C(R^1)H)_xOR^2$ (II) where R^1 and R^2 are as defined in claim 1 and x is in the range of 10-20, and mixtures thereof.

7. A composition for use according to any of the preceding claims wherein said component C is polyoxypropylene-15-stearyl ether.

8. A pharmaceutical composition for use according to claims 1 or 6, containing 0.0001 to 0.025% w/w of said component A and 0.005 to 0.1% w/w of said component B and 1 to 20% w/w of said solvent component C.

9. A pharmaceutical composition for use according to claim 1, wherein, in the treatment, the composition is applied topically once or twice daily in a medically sufficient dosage.