Patents Act 1977 **Opinion Number** **31/14**

OPINION UNDER SECTION 74A

Patent	EP 0837681 B1
Proprietor(s)	Wisconsin Alumni Research Foundation
Requester	Andrew Brown
Observer(s)	None
Date Opinion issued	03 March 2015

The request

1. The comptroller has been requested to issue an opinion as to whether the requester's product comprising paricalcitol in a 5 microgram/ml solution for injection infringes any claim in EP 0837861 B1 ("the patent") and in particular claims 1, 2, 9, 11, 12 or 14. In the event that I find this product to be infringing the requester has also asked I consider their "proposal to amend the product" to determine if this would lead me to a different conclusion. The requester has indicated that they are seeking to market the 5 microgram/ml solution of paricalcitol under a proposed marketing authorisation for the generic product. The requester has supplied a description of this product in the form of a draft Patient Information Leaflet ("PIL") and Summary of Product Characteristics ("SmPC") supplied as Appendices B and C respectively, it would appear that these document are not as yet approved by the MHRA. The requester has drawn my attention to the patent claims (appendix A) in order that I may determine if they are infringed but has also referred me to the SmPC and PIL for Zemplar (RTM) a currently marketed composition of paricalcitol, whereas these latter documents are instructive they of course have no bearing on how I determine the scope of the claims.

Observations

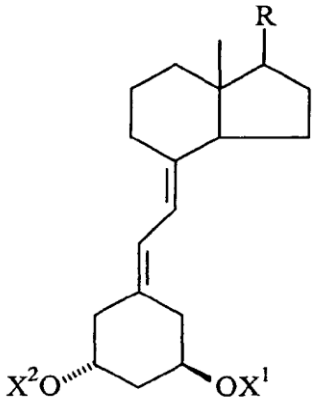
2. No observations have been submitted.

The Patent

3. The patent was filed on 9 July 2005 and granted on 6 March 2005. The invention relates to a second medical use of a vitamin D compound of formula I (see below) in the preparation of a medicament for use in the treatment of renal osteodystrophy

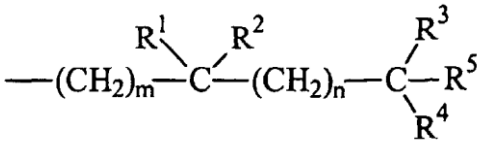
caused by a kidney disorder while avoiding vitamin D –induced hyperphosphataemia. The only independent claim, claim 1states:

Use of a 19-nor vitamin D compound of formula:



where X^1 and X^2 each represent, independently, hydrogen or a hydroxy-protecting group chosen from acyl, alkylsilyl, anylsilyl and alkoxyalkyl, and where R is represented by the structure below:

where the stereochemical centre may have the R or S configuration, and where Z is selected from Y, -OY, CH_2OY, -C≡CY and –CH=CHY, where the double bond may have the cis or trans geometry , and where Y is selected from hydrogen, methyl, CR^5O and a radical of the structure:



where m and n, independently, represent integers from 0 to 5, where R_1 is selected from hydrogen, hydroxy, protected hydroxy, fluoro, trifluoromethyl, and C1-5- alkyl, which may be straight chain or branched and, optionally, bear a hydroxy or protected-hydroxy substituent, and where each of R^2, R^3, and R^4, independently, is selected from hydrogen, fluoro, trifluoromethyl and C1-5 alkyl, which may be straight-chain or branched, and optionally, bear a hydroxy or protected-hydroxy substituent, and where R_1 and R_2, taken together represent an oxo group, or an alkylidene group, $=CR^2R^3$, or the group $-(CH_2)_P-$, where p is an integer from 2 to 5, and where R^3 and R^4, taken together, represent an oxo group, or a group $-(CH2)_q-$, where q is an integer from 2 to 5, where R^5 represents hydrogen, hydroxy, protected hydroxy, or C_{1-5} alkyl, and where any of the groups at positions 20, 22 and 23, respectively in the side chain may be replaced by an oxygen atom ***for the preparation of a medicament for the treatment of renal osteodystrophy caused by a kidney***

disorder while avoiding vitamin D-induced hyperphosphataemia. (emphasis added)

4. The latter claims refer to various compounds within the scope of Formula I (claims 2-7; various pharmaceutical forms (claims 8-10, 12 and 13) and certain dosage regimes (claims 11 and 14).

5. The background of the invention set out in paragraphs [0001]-[0003] shows the overarching aim of controlling the hormonal and metabolic effects of renal insufficiency. The resulting reducing renal mass caused by chronic kidney disease impairs the kidney's hormonal functions, among which are the synthesis of calcitriol (identified in the patent as 1, 25(OH)2D_3) this in turn leads to lower calcium absorption and a compensatory physiological response to increase parathyroid hormone release, i.e. secondary hyperparathyroidism. Secondary hyperparathyroidism is in turn one of the factors that contributes to renal osteodystrophy, wherein renal osteodystrophy is taken to mean the degenerative bone disease resulting from renal insufficiency. The background of the invention also proposes that mere replacement of calcitriol is not always indicated as it can lead to hypercalcaemia owing to increased intestinal absorption and bone demineralization which increases the serum phosphate burden already elevated as a consequence of poor clearance. The aim of the invention is to provide a vitamin D compound that suppresses parathyroid hormone (PTH) release without concomitant effects of increasing serum phosphate and calcium. These effects are confirmed in the experimental section.

Infringement

6. Section 60 Patents Act 1977 governs what constitutes infringement of a patent; Section 60(1) reads:

> *Subject to the provision of this section, a person infringes a patent for an invention if, but only if, while the patent is in force, he does any of the following things in the United Kingdom in relation to the invention without the consent of the proprietor of the patent, that is to say -*
> *(a) where the invention is a product, he makes, disposes of, offers to dispose of, uses or imports the product or keeps it whether for disposal or otherwise;*
> *(b) where the invention is a process, he uses the process or he offers it for use in the United Kingdom when he knows, or it is obvious to a reasonable person in the circumstances, that its use there without the consent of the proprietor would be an infringement of the patent;*
> *(c) where the invention is a process, he disposes of, offers to dispose of, uses or imports any product obtained directly by means of that process or keeps any such product whether for disposal or otherwise.*

7. Section 60(2) of the Act states that:

> *Subject to the following provisions of this section, a person (other than the proprietor of the patent) also infringes a patent for an invention if, while the patent is in force and without the consent of the proprietor, he supplies or*

offers to supply in the United Kingdom a person other than a licensee or other person entitled to work the invention with any of the means, relating to an essential element of the invention, for putting the invention into effect when he knows, or it is obvious to a reasonable person in the circumstances, that those means are suitable for putting, and are intended to put, the invention into effect in the United Kingdom.

8. In order to determine whether the claims of the patent would be infringed by the product, I must construe the claims of the patent, and then determine whether the product falls within the scope of the claims or relates to an essential element of the invention according to Section 60(2).

Claim construction

9. In construing the claims I will follow the well known authority on claim construction which is *Kirin-Amgen and others v Hoechst Marion Roussel Limited and others* [2005] RPC 9. This requires that I put a purposive construction on the claims, interpret it in the light of the description and drawings as instructed by Section 125(1) and take account of the Protocol to Article 69 of the EPC. Simply put, I must decide what a person skilled in the art would have understood the patentee to have intended the text of the claim to mean.

10. Section 125(1) of the Act states that:

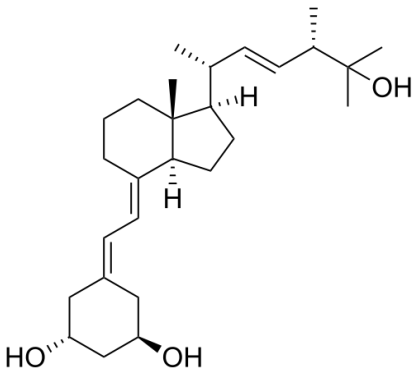
> *For the purposes of this Act an invention for a patent for which an application has been made or for which a patent has been granted shall, unless the context otherwise requires, be taken to be that specified in a claim of the specification of the application or patent, as the case may be, as interpreted by the description and any drawings contained in that specification, and the extent of the protection conferred by a patent or application for a patent shall be determined accordingly.*

11. And the Protocol on the Interpretation of Article 69 of the EPC (which corresponds to section 125(1)) states that:

> *Article 69 should not be interpreted in the sense that the extent of the protection conferred by a European patent is to be understood as that defined by the strict, literal meaning of the wording used in the claims, the description and drawings being employed only for the purpose of resolving an ambiguity found in the claims. Neither should it be interpreted in the sense that the claims serve only as a guideline and that the actual protection conferred may extend to what, from a consideration of the description and drawings by a person skilled in the art, the patentee has contemplated. On the contrary, it is to be interpreted as defining a position between these extremes which combines a fair protection for the patentee with a reasonable degree of certainty for third parties.*

12. I take the skilled person in the art to be a pharmaceutical scientist with a particular interest in the treatment of chronic/end-stage renal disease.

13. I find that the chemical structures defined by claim 1 encompass paricalcitol (see structure below), wherein the groups defined in claim 1 (set out in paragraph 4 above) are as follows: X^1 and X^2 are H and the R side chain is when $(CH_2)_m$ provides C2 alkyl, CR^1R^2 is an alkylidene group $=CR^2R^3$ when R^2 and R^3 are H and $(CH_2)_n$ is a C5 alkyl substituted by OH. Therefore I find that paricalcitol is the active ingredient of the formulation that the requester wishes to market.



14. Insofar as the patent and the requester's product both comprise paricalcitol, it remains for me to decide if the second medical use defined in the claims encompass the use the requester seeks for paricalcitol as defined in their draft SmPC and PIL (Annexes B and C respectively). I will now compare the use defined for the requester's product in these documents with that in claim 1 and decide if the use in the PIL and SmPC exhibits all of the features of the claim.

Comparison of the requester's product with claim 1

15. The request for an opinion states that the product is "indicated for the prevention of secondary hyperparathyroidism in patients with chronic renal failure undergoing haemodialysis, as set out in the SmPC and the PIL". I agree that this fairly summarises the use indicated in the requester's marketing authorisation and PIL. I find that this use is entirely within the scope of the second medical use defined in the patent claim, that use being the treatment of renal osteodystrophy caused by a kidney disorder (such as chronic kidney disease/ end stage renal failure) while avoiding vitamin D-induced hyperphosphatemia.

16. Both the use protected in claim 1 and the use of the requester's product are in the context of chronic renal disease treated by haemodialysis. As regards the specific therapeutic uses indicated, secondary hyperparathyroidism (the requester's use) and renal osteodystrophy (the use in the patent) are intimately related, secondary hyperparathyroidism being a common cause of renal osteodystrophy. The patent is replete with indications that the mode of action of the drug is mediated by its effect on reducing PTH release and as such directly treating/preventing secondary hyperparathyroidism, testament to this is the experimental evidence in Figure 1 of the patent showing that 19-nor-1, 25-(OH2)2D2 (as paricalcitol is identified in the patent) given to rats with chronic renal insufficiency produces a statistically significant and dose dependent fall in PTH.

17. The evidence that the same use underlies the requester's SmPC is found in section 5.1 of that document entitled "*Pharmacodynamic properties*" which states

"*...paricalcitol reduces parathyroid hormone (PTH) levels by inhibiting parathyroid proliferation and decreasing PTH synthesis and secretion with* ***minimal impact on calcium and phosphorous levels****, and can act directly on bone cells to maintain bone volume and improve mineralization surfaces. Correcting abnormal PTH levels, with normalisation of Calcium and Phosphorous homeostasis, may* ***prevent or treat the metabolic bone disease associated with chronic kidney disease***." (emphasis added). This section therefore clearly shows the requester's product to reduce PTH, and do so without increasing the patient's phosphate/phosphorous levels. Furthermore this section relates the fall in PTH (and treatment of secondary hyperparathyroidism) with more general metabolic bone diseases associated with chronic kidney disease. Renal osteodystrophy is plainly such a metabolic bone disease associated with chronic kidney disease. Accordingly I find that the therapeutic use of paricalcitol within the scope of claim 1 encompasses the requester's use of paricalcitol as set out in the draft SmPC and PIL and as such claim 1 is infringed having regard to Section 60(1) and Section 60(2).

18. I have also been asked to determine if claims 2, 9, 11, 12 or 14 are infringed by the requester's product. I do not find that claim 2 is infringed by the requester's product as claim 2 does not protect paricalcitol. Claim 9 is infringed as it relates to parenteral administration (i.e. administration other than via the gastrointestinal tract), the requester's product is administered intravenously, so this claim is infringed. The dosage range of claim 11 encompasses that given when administering an ampoule of the requester's product, therefore claim 11 is infringed by use of the requester's product. Insofar as the requester's product is provided in a pharmaceutically acceptable form comprising excipients, claim 12 is also infringed. Administration of phosphate binders is a routine aspect of therapy during chronic renal disease, as such, claim 14 is infringed by the routine use of the requester's product in the therapy of renal disease.

19. The final page of the request for an opinion asked that I consider if the claims would be infringed "*if the text highlighted in grey in Section 5.1 of the SmPC was removed*", this I take to be a reference to the highlighted text which states "*Correcting abnormal PTH levels, with normalization of calcium and phosphorous homeostasis, may prevent or treat the metabolic bone disease associated with chronic kidney disease*." I do not find this amendment has any bearing on whether or not the claims are infringed. It remains that the use embodied in the requester's draft SmPC is the treatment of secondary hyperparathyroidism in patients with chronic renal failure, this is irrespective of whether the quoted section of explanatory text is present or not, the presence of this text does not change the fact that the indication is the same as explained in paragraph 16.

Conclusion

20. I find at least claims 1, 9, 11, 12 and 14 of EP 0837681 B1 to be infringed by the product as set out in the request.

Jason Bellia
Examiner

NOTE

This opinion is not based on the outcome of fully litigated proceedings. Rather, it is based on whatever material the persons requesting the opinion and filing observations have chosen to put before the Office.