Patents Act 1977 **Opinion Number** **05/22**

OPINION UNDER SECTION 74A

Patent	EP(UK) 0904081 B1
Proprietor(s)	Janssen Pharmaceutica N.V.
Exclusive Licensee	-
Requester	Andrew Brown
Observer(s)	-
Date Opinion issued	28 April 2022

The Request

1. The comptroller has been requested to issue an opinion as to whether the Supplementary Protection Certificate (SPC) SPC/GB11/044, granted on 22 November 2013 and due to expire on 11 May 2022, is invalid. The requestor considers that this SPC was granted contrary to the provisions of Article 3 of Regulation (EC) No 469/2009 retained EU law. In support of this view, the requester filed the following documents with the request on 4 February 2022.:

   D1 EPAR Summary for the public for Xeplion printed on 22.10.15 (hereafter "EPAR")

   D2 Reflection paper on considerations given to designation of a single isomeric form (enantiomer), a complex, a derivative, or a different salt or ester as a new active substance in relation to the relevant reference active substance" published by the Committee for medicinal Products for Human Use 18.10.12

   D3 Directive 2001/83/EC of 6.11 2001

   D4 C-631/13 judgment of the CJEU in *Arne Forsgren v Osterreichisches Patentamt* (hereafter "*Forsgren*")

   D5 - EP 0368388 B1 (paliperidone)

   D6 - Summary of Product characteristics (Invega®)

2. The proprietor considered the references to D1 made by the requester referred to 2 different documents, the proprietor identified these and supplied the additional document as D1A, as noted below.

3. Observations were filed on behalf of the proprietor on 9 March 2022, the observations referred to the following and included further documents D7-D27:

D1A - EPAR Summary for the Public (Xeplion®)

D1 - EPAR Scientific Discussion (Xeplion®)

D7 - Summary of Product Characteristics (Xeplion®)

D8 - EMA Positive Opinion (Xeplion®)

D9 – “Gaps in use of antipsychotics after discharge by first-admissions patients with schizophrenia, 1989 to 1996” Mojtabai et al.; Psychiatric Services; March 2001; Vol. 53; No.3.

D10 - "Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: A randomized, double-blind, placebo-controlled study", Hough et al.; Schizophrenia Research; February 2010; Vol. 116; No. 2-3.

D11 - “Paliperidone extended-release tablets for prevention of symptom recurrence in patients with schizophrenia: a randomized, double-blind, placebo-controlled study” Kramer et al.; Journal Of Clinical Psychopharmacology; February 2007: Vol. 27; No.1.

D12 - EPAR Background information on the procedure (Invega®)

D13 - German Federal Patent Court decision 14W(pat) 25/16 of 5 September 2017 (German original and certified English translation)

D14 - Madrid High court of Justice decision 802/2013 of 20 April 2016 (Spanish original and English translation)

D15 - Spanish Supreme Court in decision 1140/2017 (Spanish original and certified English translation)

D16 - Athens Court of First Instance in decision 4001/2018 (Greek original and English translation)

D17 - Athens Court of Appeal decision 342/2019 of 16 January 2020 (Greek original and certified English translation)

D18 - 'EPAR summaries for the public: A further step for the provision of better information about medicines" (EPAR summaries for the public: A further step for the provision of better information about medicines | European Medicines Agency (europa.eu) and the associated Reflection Paper

D19 - "Long-acting injectable paliperidone palmitate versus oral paliperidone extended release: a comparative analysis from two placebo-controlled relapse prevention studies” Markowitz et al. Annals of General Psychiatry 2013, 12:22

D20 - A Guideline on Summary of Product Characteristics, September 2009

D21 - *Wellcome Foundation & Glaxo v Pharmachemie*, case number 343771 (Dutch original and certified translation)

D22 - Explanatory memorandum to the amended proposal for the Plant SPC Regulation (5 October 1995)

D23 - *Abraxis Bioscience LLC v The Comptroller-General of Patents* ([2017] EWHC 14 (Pat))

D24 - Report of Prof. Arango and Exhibits

D25 - Report of Dr Cowley and Exhibits

D26 - First and Second Reports of Prof .Ward and Exhibits

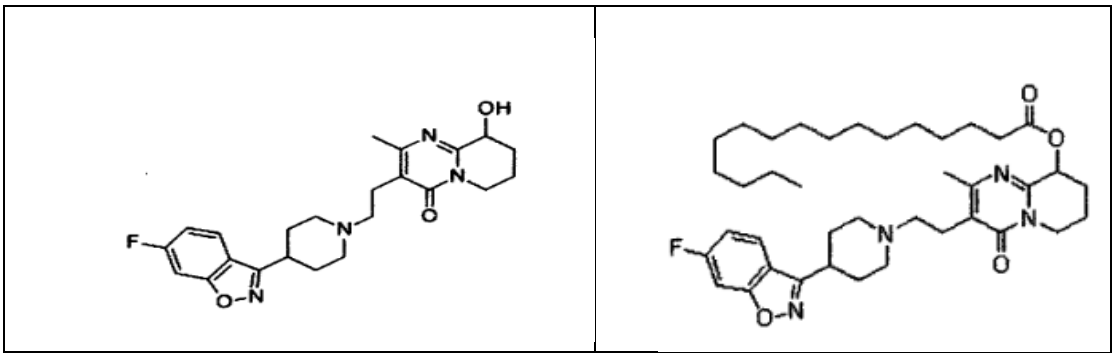
D27 – First and Second reports of Prof. Goodwin and Exhibits

4. No observations in reply were submitted. Previously, in May 2020, an opinion was requested regarding the validity of this SPC, this request was however withdrawn before an opinion was issued.

Background

5. SPC/GB11/044 is based on patent EP0904081 B1 entitled "*Aqueous suspensions of 9-hydroxyrisperidone fatty acid esters*", and marketing authorisation EU/1/11/672/001 for the medicinal product Xeplion (RTM). The qualitative and quantitative composition for Xeplion, as stated in the summary of product characteristics (D7) indicates "*Each pre-filled syringe contains 39 mg paliperidone palmitate equivalent to 25 mg paliperidone*". The request proposes that SPC/GB/11/044 is invalid having regard to SPC/GB07/065 based on EP 0368388 B1 entitled "*3-Piperidinyl-1,2-benzisoxazoles*", and marketing authorisation EU/1/07/395/001 for the medicinal product Invega (RTM), the qualitative and quantitative composition as stated in the summary of product characteristics for Invega (D6) indicates "*Each prolonged-release tablet contains 3 mg of paliperidone"*.

6. The request argues (a) that SPC/GB11/044 is invalid as this SPC and SPC/GB07/065 share an identical active ingredient paliperidone and/or (b) that SPC/GB11/044 concerns a combination of paliperidone joined covalently to palmitate, wherein the palmitate does not contribute to or create an active ingredient that has different pharmacological, immunological or metabolic activity as compared to paliperidone alone. The proposed active ingredients in these SPCs as filed and ultimately granted are:



Paliperidone SPC/GB/07/065	Paliperidone palmitate SPC/GB11/044

The requester and proprietor agree that paliperidone palmitate is an ester prodrug of paliperidone.

Forsgren C-631/13

7. The *Forsgren* judgment D4 is relevant to the question I must consider next, i.e., whether it is inappropriate to issue an opinion as provided for by Section 74A(3)(b) of the Act. Therefore, I will introduce this judgment next.

8. The facts of the *Forsgren* application are rather distant from the present SPC. *Forsgren* concerned the question of whether or not a carrier protein "protein D" could be considered an active ingredient (and as such worthy of SPC protection) even if it was covalently attached to other active ingredients and if Protein D was authorised as an active only in the context of a different therapeutic purpose. The first question in this judgment concerned the meaning of the term "product", as defined in the regulation at Article 1(b), the answer given to that question in the judgment was:

> "*Articles 1(b) and 3(a) of Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products must be interpreted as not precluding, in principle, the possibility that an active ingredient can give rise to the grant of a supplementary protection certificate where the active ingredient is covalently bound to other active ingredients which are part of a medicinal product.*"

9. This question is relevant to the present request insofar as it may bear on whether the product paliperidone palmitate should be considered as a single active ingredient or as more than one that are covalently bound to one another.

Determining if it is inappropriate to issue an opinion

10. In the proprietor's observations it was proposed that I should refuse to issue an opinion, for the reasons as summarized below:

    (a) the request seeks to establish future practice, which is not an intended use of the opinion service;

    (b) there has been litigation of the SPC equivalents in several European jurisdictions, so the level of scrutiny has already exceeded that possible in an opinion and has been maintained in every case, (with the implication that an opinion is therefore redundant);

    (c) It is inappropriate to issue an opinion so close to the expiry of the SPC, so that the holder may have to defend the SPC even after its expiry;

(d) It is vexatious; and

(e) because the request repeats arguments already addressed during examination.

I do not have the benefit of any comments in response from the requester. Therefore, I will consider each of these points in turn.

11. Taking (a)-(c) above together, I agree with the holder that the opinion service is not intended to establish future practice, but insofar as there remains the opportunity for the SPC to be challenged, I do not consider that the purpose, as alluded to in the request, should prohibit me from issuing an opinion. Indeed, the observer in recognising that the SPC may still be challenged acknowledges a valid reason for issuing an opinion. I agree with the holder that there has been a great deal of scrutiny of the equivalents of this SPC in EU jurisdictions and that, on the face of it, this weight of opinion suggests it may be difficult for the requester to persuade me otherwise. However, insofar as I am not bound to follow these judgments, I do not consider the request is redundant or vexatious for this reason. Rather, I should analyse the judgments from EU jurisdictions and determine if I am persuaded by them. Ultimately, the opinion system is intended to "*focus on the key issues in a dispute and test the strength of arguments…*" [1], this could be of benefit to litigants on either side of the validity of this SPC. Such a validity challenge is still possible, albeit late in the life of the SPC, so I do not consider it is justified that I should refuse to issue an opinion for these reasons.

12. Insofar as the proprietor also proposes that the request is vexatious in that it is identical to an opinion request filed in May 2020, I consider there are several reasons why this is not the case. Firstly, the requesters differ between the original and present request; secondly, no observations were filed in respect of the May 2020 request; and the original request was withdrawn in part to await the resolution of court proceedings, which have since been abandoned without a judgment being issued. Accordingly, an important reason for withdrawing the original request having been removed, the resubmission of the request is not considered vexatious, so I do not consider I can refuse to issue an opinion for this reason.

13. The proprietor also reminds me that I may refuse to issue an opinion if it repeats arguments already sufficiently considered. Admittedly, the observations provided pre-grant largely indicate the same arguments as in the present request. I consider the present arguments only differ substantively in respect of the discussion of the *Forsgren* judgment, see paragraph 7, this having issued since the grant of the SPC. Whereas the facts of the *Forsgren* case are admittedly distant from the present application, the answer to the first question from this judgment, see paragraph 7, nonetheless may have a bearing on the present request.

14. The requester has applied the reasoning from this answer to the first question to the facts of the present SPC – so whereas in *Forsgren* the Protein D was notionally divided from the pneumococcal polysaccharide serotypes to which it was covalently bonded, in the present case paliperidone palmitate is divided into paliperidone and palmitate. The requester considers that only paliperidone is a valid active ingredient.

[1] Paragraph 1 of the introduction to the Opinions manual

As this interpretation would, on the face of it, deem that the active has already been the subject of an SPC and, as such, would show that the SPC is invalid having regard to Article 3(c), I consider this case-law could potentially lead to a different answer to those determined in respect of the original arguments offered pre-grant. As such I do not consider that I can dismiss the *Forsgren* judgment (which is binding on me) without giving it further consideration.

What is the product

15. Before I can consider the analysis of *Forsgren* and how it applies to the present SPC, I must clarify the question to be answered. The requester states, "*it is important for the UK IPO to decide if the "active ingredient" in the SPC is "paliperidone" or "paliperidone palmitate*" and proceeds to offer arguments for each of two alternatives. Whereas, the stated active ingredient or product in the SPC application as filed and granted is clearly paliperidone palmitate, I take the requester to be asking if:

    - *Point 1*. the SPC is invalid because it was granted for a product, paliperidone and another substance - palmitate. The requester supports this view by reference to the authorisation to show that is in fact for paliperidone. The SPC would accordingly be invalid in respect of Article 3(c) as the SPC for Invega and Xeplion would in fact be for the same product; or

    - *Point 2.* the SPC is invalid because the combination of paliperidone and palmitate does not create a new product or does not comprise a combination of products that has a different pharmacological, immunological or metabolic action (as compared to paliperidone alone.

    Whereas points 1 and 2 overlap, given that they are both rely on dividing paliperidone palmitate into independent active ingredients/substances, I will consider them separately.

Analysis

16. Turning to point 1, I have considered the requesters argument that the purpose of the regulation is to award SPCs to new medicinal products and not develop variants - different forms of a product with no substantial difference in therapeutic or pharmacological properties, the requester supports their view that paliperidone palmitate is merely a variant of the drug paliperidone by reference to the Regulator's guidance surrounding new active substance (NAS) status set out in D2, and finding that paliperidone palmitate does not have NAS status.

17. I do not consider new active substance status to be a definitive criterion under the regulation. Whereas it may be expected that variants not worthy of an SPC would also not qualify as a NAS, this does not mean an SPC may not be awarded or is invalid if it is not for a NAS. I note that the requesters conclusion that paliperidone palmitate is not a NAS rests on a reference from the EPAR for Xeplion (D1) that indicates the active ingredient in Xeplion is paliperidone, however other references in this document indicate the active substance to be paliperidone palmitate, so it is not

clear to me that the authorisation is for the active ingredient paliperidone alone. I have also considered the EPAR documents and SmPC for Xeplion, I consider that insofar as they show the results of short and long studies "to evaluate the safety and efficacy" of paliperidone palmitate, I am not persuaded to place particular weight on a reference to paliperidone as the active ingredient, rather the authorisation substantiates that the product authorised is paliperidone palmitate. Therefore, I am not persuaded this SPC is invalid as it has not been afforded NAS status, and is in fact based on an authorisation for paliperidone, as argued under point 1.

18. Point 2 is based on applying the reasoning of the answer to the first *Forgsren* question to the present SPC, see paragraph 14.

19. At its heart the argument as regards point 2 concerns what is the nature of product in this case as this is informed by *Forsgren*. *Forsgren,* as pointed out by the requester and proprietor, relies on the reasoning of the earlier judgment in *Massachusetts Institute of Technology* (MIT) to determine what is meant by product when it states at paragraph 25 & 26 of the judgment as follows:

> *"25. It follows that the term 'active ingredient', for the purposes of applying Regulation No 469/2009, concerns substances producing a pharmacological, immunological or metabolic action of their own. Since Regulation No 469/2009 does not draw any distinction according to whether an active ingredient is covalently bound with other substances, it is not appropriate to exclude, on that ground, the grant of an SPC for such an active ingredient.*
>
> *26. On the other hand, the Court has held that a substance which has no therapeutic effect of its own and which is used to obtain a certain pharmaceutical form of the medicinal product is not covered by the term 'active ingredient' and, consequently, cannot give rise to the grant of an SPC (judgment in Massachusetts Institute of Technology, EU:C:2006:291, paragraph 25)."*

20. The requester considers paliperidone is the active ingredient as it produces a pharmacological effect, whereas the palmitate although it has "*some effect in the performance of paliperidone by changing its* ***physical properties*** *to allow it to deliver paliperidone over a sustained period of time, palmitic acid* [palmitiate moiety] *has no effect on the pharmacological properties of paliperidone*", and so, in line with MIT, the requester proposes the SPC for paliperidone palmitate is invalid, as the palmitate has no therapeutic effect of its own.

21. It appears to be an attractive argument that a prodrug such as paliperidone palmitate can suitably be divided into an ultimately active metabolite (paliperidone) and a carrier (palmitate) which in use is intended to alter the pharmacodynamic properties of the active. One can imagine diminishing differences between a parent active ingredient and variants or derivatives that share the activity of the parent molecule entirely or substantially so as not to justify an SPC.

22. However, I do not consider this interpretation of *Forsgren* is ultimately persuasive. The wording of the answer to the first question in *Forsgren* is permissive, it details reasoning wherein SPCs may be allowed (for actives covalently bonded to other actives); it is not prohibitory - it does not set out criteria by which products should be

subdivided to protect only the smallest part that has "pharmacological, immunological or metabolic action". The additional answers in *Forsgren* predicated on the answer to the first question do not change my view, I do not consider that *Forsgren* deems that prodrugs, such as paliperidone palmitate, should not be afforded SPC protection. Therefore, I am not persuaded by the requester's interpretation of *Forsgren* to support their view in point 2.

23. Furthermore, I consider the argument based on *Forsgren* is yet less tenable because there are clear reasons to find to the contrary. I will consider these reasons next. Firstly, there is a clear and specific legal basis to show that the requesters interpretation of *Forsgren* is incorrect having regard to recital 14 of Regulation 1610/96 which states:

> *"…the issue of a certificate for a product consisting of an active substance does not prejudice the issue of other certificates for derivatives (salts and esters) of the substance, provided that the derivatives are the subject of patents specifically covering them*"

This provision, which remains relevant for the interpretation of the retained law by virtue of recital 17 of Regulation 469/2009, is directly applicable to the present circumstances - the present SPC for paliperidone palmitate should not be prejudiced by the earlier SPC for paliperidone as the present SPC is based on a basic patent for paliperidone palmitate - see claim 2 of EP(UK) 0904081 B1.

24. Secondly, I have also considered the judgments of the courts from various EU jurisdictions furnished as D13-D17, and I have found that they are all predicated on a conclusion that paliperidone palmitate has distinguishable therapeutic effects as compared to paliperidone, these effects such as delayed release and the consequent clinical benefit of preventing gaps in treatment justify the courts' finding that paliperidone palmitate is a different product as compared to paliperidone. Turning to how EU jurisdictions have considered the *Forsgren* judgment[2], they concluded, having regard to paragraph 25 (as quoted in paragraph 19 above) in particular, that paliperidone palmitate is a substance producing a pharmacological, immunological or metabolic action of its own. None of these courts have been persuaded to refuse the equivalents to the present SPC in their respective jurisdictions. This all represents highly significant support for the validity of the present SPC.

25. I have also briefly considered the witness statements D24-D27 and literature references D9-D11 provided with the observations to consider if they support the view that paliperidone palmitate has a distinguishable therapeutic effect as compared to paliperidone. I have considered the witness statements with some caution as I have no statements provided by the requester advancing an opposite view, but they nonetheless show a convincing picture that paliperidone palmitate has provided a real clinical benefit to schizophrenia patients over and above paliperidone alone. Whereas this is not itself determinative that the SPC is valid, it does not support the requesters view that the palmitate is a mere variant, on the contrary they support the view that the MA is for a different active, and has been authorised as

[2] the lower Athens court gives Forsgren no consideration, but each of the German, Spanish, Spanish Appeal court, and the Athens appeal court do

such by the regulator (see paragraph 17).

Summary and Conclusion

26. In summary, I have analysed the requesters arguments that the SPC for paliperidone palmitate is invalid as paliperidone palmitate is a mere variant of paliperidone, because it does not have NAS status, and that the palmitate portion of the active should be considered independently that to show no pharmacological, immunological or metabolic action of its own in line with the requester interpretation of *Forsgren*. I have not been persuaded by any of these arguments. Rather I consider the authorisation documents on balance support the view that the authorisation is for the active paliperidone palmitate and that recital 14 of regulation 1610/96 shows the earlier SPC for paliperidone should not prejudice the validity of the present SPC. I have also found that the judgments from EU jurisdictions considering the validity of the equivalents to this SPC have unanimously supported the view that this SPC is valid. I have considered the arguments in these judgments and agree with their conclusions.

27. Therefore, I consider SPC/GB11/044 to be valid.

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.