Decision in Respect of a Request by Roche Glycart AG for the Grant of a Supplementary Protection Certificate (SPC) No. 2017/044

INTRODUCTION

1. This decision concerns a request for the grant of SPC application no. 2017/044 filed on 26 October 2017 on behalf of Roche Glycart AG by FRKelly in respect of "*Gazyvaro - obinutuzumab in combination with bendamustine*".

2. The original legislation governing SPCs is Council Regulation (EEC) No. 1768/92 relating to *"the creation of a supplementary protection certificate for medicinal products"*. This was subsequently amended and codified in Regulation (EC) 469/2009 – hereinafter, the *"*SPC Regulation*".* The legislation governing the authorisation of medicinal products is Directive 2001/83/EC relating to "*medicinal products for human use"* – hereinafter, the *"*Medicinal Products Regulation*".*

3. In the application, the product (*'the active ingredient or combination of active ingredients of a medicinal product'* as defined in Article 1 (b) of the SPC Regulation) for which a certificate was requested was "*obinutuzumab in combination with bendamustine*".

4. Patent no. EP 2 464 382 *('Combination therapy of an afucosylated CD20 antibody with bendamustine'*) was cited as the "basic patent" in support of the request, as required by Article 1(c) of the SPC Regulation.

5. A copy of the Commission Decision of 13 June 2016 issued by the EC amending the original marketing authorisation (MA) of 23 July 2014 for *"Gazyvaro – obinutuzumab"* was also submitted. Attached to this document was a copy of the amended annexes, in particular the amended Summary of Product Characteristics (SmPC) to account for the changes arising from what is known as a "Type II variation" to the original MA.

6. In the letter accompanying the application, the agent explained that, rather than a new authorisation being issued for this new combination, the original MA for *obinutuzumab* had been amended by way of such a Type II variation. The agent explained that for this to happen, additional major clinical studies using the new combination treatment had had to be carried out in accordance with the Medicinal Products Regulation. He argued that such a variation to the original MA should therefore be deemed to have met the requirement of Article 3(b) of the

SPC Regulation. In support he cited a ruling by the Higher Regional Court of Vienna (Decision 34 R 104/15) that stated, in the light of the CJEU judgment in the *Neurim* case (C130-11), a Type II variation could be considered as a valid MA for the purposes of Article 3(b).

7. In her reply of 3 October 2018, the examiner noted that the amended authorisation provided for a new therapeutic indication namely, the treatment of follicular lymphoma in which *obinutuzumab* was being used in a combination therapy with *bendamustine*. However, she observed that, while the SPC application sought protection for the product *obinutuzumab in combination with bendamustine*, the reissued MA still related explicitly to the single product, *Gazyvaro – obinutuzumab*, i.e. to a single active ingredient. She stated that this amended authorisation could not be construed as one to place the product *obinutuzumab in combination with bendamustine* on the market. She concluded by proposing to reject this SPC request owing to non-compliance with Article 3(b).

8. The examiner also remarked that the applicant had already obtained an SPC (No. 2016/009) for *obinutuzumab*, based on the original MA (EU/1/14/937/001). Noting the provision in Article 4 of the SPC Regulation - *"Subject-matter of Protection"* - she commented that the protection afforded by this SPC to *obinutuzumab* would also extend to it being used together with *bendamustine* for the treatment of follicular lymphoma.

9. The agent responded on 28 January 2019 to argue that an SPC should be available for a new combination of two active ingredients which are not formulated as a "fixed", but rather a "loose", combination. In support, he cited a comment in the CJEU judgment in *Neurim* referring to a "teleological approach" when interpreting Article 3 of the SPC Regulation. The agent then went on to emphasise the extensive clinical trials which had been carried out, and which should therefore warrant SPC protection being conferred on the combination product.

10. In the matter of the "loose" combination of *obinutuzumab* and *bendamustine*, the agent explained that the amended MA made it clear it was mandatory for *obinutuzumab* to be used in combination with *bendamustine* for a particular therapeutic use, namely the treatment of follicular lymphoma. The agent also commented that, had this particular combination resulted in a new fixed dose administration, then a separate MA would undoubtedly have been granted and its eligibility for SPC protection would have been "acte claire". The agent cited the CJEU judgments in *Medeva* (C-322/10) and *Georgetown* (C-433/10) as evidence of a more balanced or "teleological" approach to the interpretation of Article 3(b). Likewise, the agent argued that the "guidance" provided by the CJEU in both *Medeva* and *Neurim* was also applicable to

"loose" combinations of active ingredients.

11. In conclusion, the agent requested the examiner to reconsider her opinion or to stay the case should she continue to have any remaining concerns because there were pending equivalent SPC requests in other EU Member States, and there was also a likelihood of the case being referred to the CJEU at some point.

12. The examiner responded on 31 August 2020 and drew the agent's attention to the CJEU judgment in *Santen* (C-673/18) which had issued in the intervening period, and in which the court had set aside its own decision in *Neurim* in a clear and unambiguous manner. She concluded by restating her objection under Article 3(b) and her intention to reject the SPC request.

13. The agent replied on 8 October 2020 to request a hearing and this was arranged for 12 November 2020. Because of the ongoing Coronavirus pandemic and with the IPOI still closed to the public, it was agreed that the hearing would take place by videoconference. The applicant was represented by Donal Kelly and Con O'Connor (both from FRKelly). On the IPOI side, in addition to myself and Dolores Cassidy (who handled the case), Fergal Brady (another SPC examiner) also participated.

14. In advance of the hearing, the agent submitted a detailed pre-filing submission setting out his reasoning in support of the grant of the SPC request.

ANALYSIS

15. Much of the hearing focussed on the examiner's primary objection to the agent's assertion that the Type II variation to the original MA for *Gazyvaro – obinutuzumab* could be deemed to have met the Article 3(b) provision of the SPC Regulation.

16. In relation to the CJEU judgment in *Santen*, the agent argued that this did not affect the current case because the SPC request was based on a new product, namely the combination of *obinutuzumab* and *bendamustine*. I believe, however, that the *Santen* decision is highly relevant. The amended MA in this case provides for a new therapeutic indication using the active ingredient, *Gazyvaro – obinutuzumab*, the subject of the authorisation, albeit in combination with *bendamustine*. The judgment in *Santen* makes it very clear that a later MA for a new therapeutic indication cannot be used as the first MA in support of a subsequent

SPC request for a new medical use based on an active ingredient which has already been the subject of an earlier SPC.

17. Clearly, the authorisation, as amended on page 2 of Annex I under Section 4.1 – "Therapeutic indications", provides for the administration of *Gazyvaro* with *bendamustine* for the treatment of patients with follicular lymphoma. This amendment to the original MA, however, does not mean that *bendamustine* somehow becomes a fundamental part of the MA in the way that *Gazyvaro* clearly is. What it does do is to provide necessary information to define a new therapeutic application for *Gazyvaro* and to highlight and detail the additional clinical trials that were necessary for its use with *bendamustine* to be approved for the particular cancer treatment.

18. However, as the "Commission Implementing Decision" indicates on the cover page of the document, the amended MA clearly relates specifically to the product "*Gazyvaro – obinutuzumab*". I take this to mean that the only active substance, as far as the MA is concerned, is just that very product and, as such, this MA cannot be considered as one for a combination product of *obinutuzumab* with *bendamustine*. This combination relates specifically to the stated therapeutic indication in Annex I. Therefore, it is clear to me that the examiner was correct in asserting that this amended MA cannot be considered as a valid authorisation and I conclude that the application does not meet the requirements of Article 3 (b) of the SPC Regulation.

19. Although the examiner did not raise any objection under Article 3(a) of the SPC Regulation, the agent did raise it in some detail in the pre-filing submission and it was briefly discussed at the hearing.

20. As mentioned briefly in paragraph 4, the invention disclosed in the basic patent is directed to the combination therapy of an afucosylated anti-CD20 antibody with *bendamustine* for the treatment of the cancer, follicular lymphoma; and especially to the combination therapy of CD20 expressing cancers with an afucosylated humanized B-Ly1 antibody and *bendamustine*.

21. Claim 1 of the patent is a 'Swiss-type' claim i.e. a purpose-related process claim as provided for under the EPC (1973) - such claims are allowable in applications filed before 29 January 2011, as in this case.

1. Use of an afucosylated anti-CD20 antibody with an amount of fucose of 60 % or less of the total amount of oligosaccharides (sugars) at Asn297, for the manufacture of a medicament for the treatment of cancer in combination with bendamustine, characterized in that said cancer is a CD20 expressing cancer and in that said antibody comprises an amino acid sequence of the variable region of the heavy chain (VH) of SEQ ID NO: 7, and an amino acid sequences of the variable region of the light chain (VL) of SEQ ID NO: 20.

Claim 1 is directed to the use of a specific afucosylated anti-CD20 antibody for the manufacture of a medicament for the treatment of certain types of cancer in combination with *bendamustine*, and not to the use of the combination of this particular antibody and *bendamustine* for the manufacture of a medicament for the same treatment. To be clear, it is the use of the antibody (*obinutuzumab*) in the particular circumstance of its being combined with *bendamustine* that is protected by this claim, and not the combination itself.

22. The other independent claim in the patent is Claim 6, which is a purpose-related product claim as provided for under Article 54(5) EPC (2000).

6. An afucosylated anti-CD20 antibody with an amount of fucose of 60 % or less of the total amount of oligosaccharides (sugars) at Asn297, for use in the treatment of cancer in combination with bendamustine, characterized in that said cancer is a CD20 expressing cancer and in that said antibody comprises an amino acid sequence of the variable region of the heavy chain (VH) of SEQ ID NO: 7, and an amino acid sequences of the variable region of the light chain (VL) of SEQ ID NO: 20.

Claim 6 is directed to a product - a specific afucosylated anti-CD20 antibody - for use in the treatment of certain types of cancer in combination with *bendamustine*, and not the combination itself.

23. In conclusion, I conclude that the basic patent, EP 2 464 382, only protects a single product as evidenced by Claim 6 – the particular afucosylated anti-CD20 antibody specified in the characterising part of the claim. This claim also limits the use of this antibody to a specific application, namely for the treatment of certain types of cancer in combination with *bendamustine*. As mentioned previously, the applicant has already obtained an SPC for this particular product, *obinutuzumab,* based on the original authorisation and an earlier patent, EP 2 380 910.

24. As stated in paragraph 18, I believe that the amended MA cannot be considered as a valid authorisation for the product "*Obinutuzumab in combination with Bendamustine*" and therefore the application does not meet the provisions of Article 3 (b) of the SPC Regulation.

DECISION

The request for the grant of Supplementary Protection Certificate No. 2017/044 by Roche Glycart AG for the product *"Obinutuzumab in combination with Bendamustine"* is rejected under Article 10(2) of the SPC Regulation.

Dr. Michael Lydon

Hearing Officer

19 January 2021