European Ombudsman

Decision in case 1421/2017/JAS on the European Medicines Agency's alleged failure to address concerns about a pharmaceutical product

Decision
Case 1421/2017/JAS - **Opened on** 14/12/2017 - **Decision on** 14/12/2017 - **Institution concerned** European Medicines Agency (No maladministration found) |

This case is about the European Medicines Agency's (EMA) handling of concerns raised by the complainant about a particular medicine.

The Ombudsman may examine if a scientific body complies with all procedural requirements imposed on it. This includes the need for the body to show that it has examined all relevant information submitted to it. Regarding the scientific assessments of that information, it is not the role of the Ombudsman to question the merits of scientific evaluations carried out by specialised scientific bodies.

Regarding the evaluation of the complainant's concerns about a particular medicine, the Ombudsman found that EMA's Pharmacovigilance Risk Assessment Committee (PRAC) had assessed the concerns raised by the complainant in the context of the annual report on that medicine's safety. PRAC took the information provided by the complainant very seriously and took what it considered to be the appropriate action.

The Ombudsman concludes that there was no maladministration by EMA in the handling of the complainant's concerns .

Background to the complaint

1. The European Medicines Agency (EMA) recognises that progressive multifocal leukoencepahlopathy (PML) [1] , a viral disease which is usually fatal in patients with severe immune deficiency, is a very rarely occurring side effect [2] of taking rituximab, a medicine used to treat blood cancers and inflammatory conditions such as severe rheumatoid arthritis [3] .

2. The complainant, a biologist and himself a cancer patient, argues that the incidence of PML in patients using rituximab is higher than the official estimates. He also argues that there is a link between PML and low levels of CD4 (a type of white blood cell) in patients treated with

rituximab. He takes the view that the so-called “Stratify JCV” test should also be used for patients receiving rituximab. The complainant has been in contact with EMA on this issue since early 2017. In support of his arguments, the complainant provided EMA with the results of various scientific studies.

3. In March 2017, EMA informed the complainant that the Pharmacovigilance Risk Assessment Committee (PRAC) [4] , EMA’s committee responsible for monitoring the safety of human medicines already on the market, was evaluating the latest “periodic safety update report” for rituximab. A “periodic safety update report” is a report provided to EMA, at regular intervals, by the company marketing a medicine. It contains an evaluation of the benefit-risk balance of a medicine and includes the results of all studies carried out with the medicine, both in its authorised uses and in unauthorised uses. EMA uses the information in a periodic safety update report to determine if there are new risks identified for a medicine or whether the balance of benefits and risks of a medicine has changed. It can then decide if further investigations need to be carried out or can take action to protect the public from the risks identified, such as updating the information provided for healthcare professionals and patients [5] .

4. EMA stated that PRAC would consider the issues raised by the complainant and the documentation provided by the complainant.

5. In April 2017, senior staff of EMA met with the complainant to clarify how his concerns were being addressed.

6. In June 2017, PRAC issued its assessment of the periodic safety update report on rituximab [6] . PRAC took the view that the benefit-risk balance of rituximab remained unchanged [7] . However, PRAC requested the company marketing the medicine (the so-called marketing authorisation holder) to provide further information within three months. It also asked the marketing authorisation holder to carry out an in-depth review of all risk factors for PML in rituximab treated patients.

7. The complainant was not satisfied with the results of the assessment and turned to the Ombudsman in August 2017.

The inquiry

8. The Ombudsman opened an inquiry into the complaint. The complainant’s position is that EMA failed to properly address his concerns about the possible side effects of the medicine rituximab.

9. In the course of the inquiry, the Ombudsman duly considered the information provided by the complainant as well as other publicly available information.

EMA’s handling of the complainant’s concerns

Arguments presented to the Ombudsman

10. The complainant argued that PRAC had not properly dealt with the issues he had raised. He claimed that EMA had failed to treat the information he had provided as a so-called “signal”. A “signal” is information of sufficient relevance to suggest a new causal association between a medical intervention and an event. The “event” can be either adverse or beneficial [8] .

11. The complainant, in support of his complaint, stated that some of the information he had provided to EMA was ignored by PRAC. He noted that one of the studies he had referred to had not been mentioned in PRAC’s assessment of the periodic safety update report. He also claimed that PRAC had rejected the results of one study without giving any reasoning.

The Ombudsman's assessment

12. The Ombudsman does not consider that PRAC failed to take proper account of the information provided by the complainant. She bases this finding on the fact that PRAC, in its assessment of the periodic safety update report, explicitly mentions and assesses the complainant’s arguments and concerns.

13. Regarding his first concern, the incidence of PML, PRAC stated: “ *The* **third party intervention** [[9]] *suggested that the incidence/frequency of PML* [...] *does not provide a true and fair presentation of the data.* **The following references were provided by the third party** *:* [...]” (emphasis added). One of the references mentioned by PRAC is the study that, according to the complainant, had been ignored.

14. PRAC stated further: “ *The references provided by the third party* **were considered by the PRAC** *and do not allow on its own to calculate the true incidence of PML* [...] *; nor* [does] *the data provided in the individual* [periodic safety update report] *and the cumulative review”* allow for such a calculation.

15. The PRAC thus concluded that the *“* **[marketing authorisation holder]** *should review the incidence of PML in rituximab treated patients and stratified by indication and clinical setting* [...] *using all available information. This review should include all available literature data,* **including the above references** [that is, the documentation provided by the complainant, including the study he considers essential]” (emphasis added).

16. Regarding the complainant’s second concern, low levels of CD4 in patients treated with rituximab, PRAC stated: “ *During* [the periodic safety update report] *preparation the* [marketing authorisation holder] *was requested to further analyse and comment on a previous signal “CD4 Lymphocyte percentage decreased” closed in the last* [periodic safety update report] *.* [...] *Overall, based on the assessment of all of the data provided, the PRAC considers that the* **signal "CD4 lymphocytes decreased" should be reopened and further discussed** *by the*

[marketing authorisation holder] . *Hence, the* [marketing authorisation holder] *is requested to provide a* **cumulative review** *of* [CD4] *decrease overall* [...] *addressing all relevant data (spontaneous, clinical trials, literature) split by indication.* [...] *The* **impact of this review on the benefit-risk balance of the products should also be discussed** *and any relevant proposals to update the* [summary of product characteristics] *should be made* " (emphasis added).

17. Regarding the complainant's third concern, the possible use of the "Stratify JCV" test, which is currently used for another medicine (natalizumab), PRAC stated: " *During this* [Periodic safety update report single assessment] *procedure, the* **third party** *also indicated that anti-JCV antibody testing (STRATIFY JCV) should be used as a risk minimisation measure in* [rituximab] *treated patients.* [...] *StratifyJCV has not been validated for the patient populations treated with rituximab* [...] *who present different immunocompetence challenges than natalizumab-treated patients and whether these conclusions can be extrapolated to rituximab-treated patients is unknown.* [...] *Further data are needed to assess whether rituximab patients can be stratified for the risk of developing PML using JCV diagnostic tests* [...] . *Hence the* [marketing authorisation holder] *is* **requested to review all risk factors for PML in rituximab treated patients** , *discuss the need for PML risk stratification strategies, and make a proposal for a risk stratification algorithm. In particular, the* [marketing authorisation holder] *should* **discuss the usefulness of JCV diagnostic assays** [...]" (emphasis added).

18. In June 2017 PRAC requested the marketing authorisation holder to provide its response within three months [10] . At its July 2017 meeting, PRAC decided to seek advice from an ad-hoc expert group in the context of the procedure [11] .

19. The complainant also argued that EMA should have handled his concerns in accordance with Commission Implementing Regulation 520/2012 [12] and EMA's internal rules on signal management for centrally authorised products based on that Regulation [13] .

20. The Ombudsman notes that it is PRAC that is responsible for analysing and prioritising signals [14] . Any work by EMA's staff on signal management relates to *identifying* potential signals that warrant analysis by PRAC [15] . Since the concerns put forward by the complainant were **already** under assessment by PRAC, there was no need for EMA staff to take such preparatory action. The Ombudsman also notes that PRAC explicitly stated that " *the* **signal "CD4 lymphocytes decreased" should be reopened** " (emphasis added).

21. The Ombudsman thus concludes that PRAC took the information provided by the complainant very seriously indeed and acted upon it. Furthermore, it is clear that PRAC will revisit the complainant's concerns on the basis of the additional data to be provided by the marketing authorisation holder.

22. The complainant does not agree with all of PRAC's scientific conclusions. However, the Ombudsman does not question the merits of scientific evaluations carried out by specialised scientific committees such as PRAC [16] .

Conclusion

Based on the inquiry, the Ombudsman closes this case with the following conclusion [17] :

There was no maladministration by the European Medicines Agency in its handling of the complainant's concerns about possible side effects of the medicine rituximab.

The complainant and the European Medicines Agency will be informed of this decision **.**

Emily O'Reilly

European Ombudsman

Strasbourg, 14/12/2017

[1] More information available at:
https://www.ninds.nih.gov/Disorders/All-Disorders/Progressive-Multifocal-Leukoencephalopathy-Information-Page
[Link]

[2]
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000165/WC500025
[Link]

[3]
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000165/human_med_000897.jsp
[Link]

[4]
http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000537.jsp
[Link]

[5] More information available at:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000361.jsp
[Link]

[6] PRAC Periodic safety update report EMA/PRAC/345796/2017.

[7] PRAC Minutes of the meeting on 6-9 June 2017, EMA/PRAC/478147/2017, pages 37-39, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2017/07/WC500232398.pdf [Link]

[8] See Article 19 of Regulation Commission Implementing Regulation (EU) No 520/2012 (Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council, OJ 2012 L 159, p. 5, available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:159:0005:0025:EN:PDF [Link]).

[9] The Ombudsman assumes that this refers to the complainant.

[10] In the framework of a dedicated procedure, a so-called legally binding measure. More information available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000037.jsp&mid=WC0b0 [Link]

[11] PRAC Minutes of the meeting on 6-9 June 2017, EMA/PRAC/478147/2017, page 39, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2017/07/WC500232398.pdf [Link]

[12] In particular, Article 21 of Commission Implementing Regulation 520/2012. See footnote 8.

[13] EMA standard operating procedure on signal management for centrally authorised products, SOP/H/3065, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Standard_Operating_Procedure_-_SOP/2009/09/WC500 [Link]

[14] Article 21(5) in connection with Article 28a(2) of Regulation 726/2004 (Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ 2004 L 136, p. 1, consolidated version available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2004R0726:20120702:EN:PDF [Link]): " *The* **Pharmacovigilance Risk Assessment Committee** *shall perform the initial analysis and prioritisation of signals of new risks or risks that have changed or changes to the risk-benefit balance. Where it considers that follow-up action may be necessary, the assessment of those signals and agreement on any subsequent action concerning the marketing authorisation shall be conducted in a timescale commensurate with the extent and seriousness of the issue* " (emphasis added).

[15] See, for example, page 9 of EMA standard operating procedure on signal management for centrally authorised products, link available in footnote 13.

[16] Decision in case 1475/2016/JAS on the European Medicines Agency's handling of the referral procedure relating to human papillomavirus (HPV) vaccines, paragraph 21, available at: https://www.ombudsman.europa.eu/en/cases/decision.faces/en/84736/html.bookmark [Link]

[17] Information on the review procedure can be found on the Ombudsman's website: http://www.ombudsman.europa.eu/en/resources/otherdocument.faces/en/70669/html.bookmark [Link]