Analysis of the WHO forms submitted by the MSIF panel members on Azathioprine and Rituximab as treatments of Multiple Sclerosis

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EAN Ethics and Quality Task Force

This analysis has been made on the request of MSIF that needed an independent and respected organisation to review the conflict of interest declarations of the panel members. More specifically, EAN has been asked to evaluate whether the panel members would need to be recused from a particular recommendation or not to participate at all. The EAN Ethics and Quality Task Force is judging according to EAN-rules approved for Guideline Production task forces.

The MSIF panel members are:

1. Najoua Abkari
2. Kathleen Costello
3. Nicola De Stefano
4. Gavin Giovannoni
5. Tapas Kumar
6. Aukje Mantel-Teeuwisse
7. Gloria Mutinta
8. Thomas Piggott
9. Andrea Prato
10. Tamara Pringsheim
11. Nick Rijke
12. Mohammad Sahraian
13. Deanna Saylor
14. Holger Schunemann
15. Fatima Suleman
16. Shanthi Viswanathan Shanthakumar
17. Bassem Yamout
18. Maya Zeineddine

The WHO forms **«** Declaration of interests for WHO experts » as filled by the panel MSIF members have been sent to the EAN Ethics and Quality Task Force members on 11 December 2020.

These forms include 4 chapters:

1. Identifying information
2. The work under consideration for publication including
    - Employment and consulting (1a and 1b)
    - Research support (2a and b)
    - Investments interests (3a and b)

- Intellectual property (4a and b)

3. Public statements, positions and additional information
   - Public statements and positions (during the last three years) (5a and b)
   - Additional information (6a to e)
   - Tobacco or tobacco products (answer without regard to relevance to the subject of the meeting or work) (7a)
4. Declaration
   - DECLARATION I hereby declare on my honour that the disclosed information is true and complete to the best of my knowledge
   - Should there be any change to the above information, I will promptly notify the responsible staff of WHO and complete a new declaration of interest form that describes the changes. This includes any change that occurs before or during the meeting or work itself and through the period up to the publication of the final results or completion of the activity concerned.

Furthermore, the panel members had to sign the MS international federation non-disclosure agreement slightly modified at request from the EAN Ethics Committee to include in §2 *« On the form you should include information on any contributions to the development or research associated with azathioprine, rituximab and other anti-CD20 monoclonals in part 6e* ».

Notice that these signed forms have not been communicated to the EAN Ethics and Quality Task Force.

All panels members answered NO to all items of the WHO forms except:

- Nicola de Stefano
  - Item 6d: Have you received any payments (other than travel costs) or honoraria for speaking publicly on the subject of this WHO meeting or work?
    - *I have been in the Speaker bureau for Biogen, Sanofi-Genzyme, Merck,* ***Novartis****, Teva,* **Roche***, Celgene (all drug companies involved in MS)*
- Gavin Giovannoni
  - Item 1b: Within the past 4 years, have you received remuneration from a commercial entity or other organization with an interest related to the subject of the meeting or work?
    - *Consulting, including service as a technical or other advisor*
    - *Abbvie, Actelion, Biogen, Celgene, Genentech, GSK, GW Pharma, Janssen, Merck-KGaA,* ***Novartis****,* ***Roche****, Sanofi-Genzyme, Teva.*
    - Personal
  - Item 2a: Within the past two years, have you or has your research unit received support from a commercial entity or other organization with an interest related to the subject of the meeting or work?
    - *Research support, including grants, collaborations, sponsorships, and other funding*
    - *Takeda,* ***Roche****, Merck-KGaA*
    - *Employer*

- Item 5a: Public statements and positions (during the last 3 years):
  - *As part of a regulatory or judicial process, have you provided an expert opinion or testimony, related to the subject of the meeting or work, for a commercial entity or other organization?*
  - *Expert opinion in relation to fingolimod's EU patent. I was a consultant for a third-party (Brtows Law firm) and the consultancy fees were paid for by* ***Novartis****.*

– Mohammad Ali Sahraian
  - Item 6a: Additional information
    - *Is there any aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence?*
    - *I have been principal investigator for a clinical trial comparing* ***Ocrevus*** *with generic one and have been paid for this trial by Cinnagen Company*

All panel members ticked **the two boxes of the « Declarations » at the end of the WHO form.**

Discussion and conclusion

EAN internal document:
Managing conflicts of interest for the task forces for Guideline Production
(version 26.03.2019)

…
The purpose of managing conflicts of interest (COI) is to exclude unwanted influence from all kind of unauthorized stakeholders in the field of managing patient care. This may be typically industry wanting its products to receive favourable judgment by the final guideline product, but also non-physician managers dealing with healthcare in hospitals, governmental bodies judging on healthcare approval of medical products or services, health insurance companies and other stakeholders in the broader field of healthcare.
…
Typically, an individual having a CoI in a special area should have the right to speak on this topic and to help writing the specific topics but not to vote on the final acceptance of the recommendation. There is also the possibility that the GL-member who is involved in a specific question should not write the appropriate part of the GL.
…

Azathioprine, the prodrug 6-mercaptopurine, was synthetized in 1957 and is marketed since several decades as an immunosuppressant. Analysis of the WHO forms completed by the MSIF panellists does not reveal any conflict of interest.

Rituximab is a monoclonal antibody directed to the CD20 antigen. To the best of our knowledge, two other anti-CD20-antibodies are or will be available for the treatment of MS: **Ocrelizumab** (Roche) and **ofatumumab** (Novartis).
As three panellist mention having received honoraria from the companies (Roche and Novartis) who are or will be commercializing these two monoclonal antibodies, the EAN ethics committee considers that the same rule as they used for the EAN guideline production group should be applied:

Panellists Nicola de Stefano, Giovannoni Gavin and Mohammad Ali Sahraian should have the right to speak on the topic of Rituximab but not to write the corresponding part of the panel report nor to vote on the final acceptance of the panel recommendation.


Günther DEUSCHL


Maria STAMELOU


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