27th of November 2020

Dear WHO Expert Committee on Essential Medicines,

The Multiple Sclerosis International Federation would like to acknowledge and thank the WHO Expert Committee for the feedback received in 2019 for our application to add disease modifying therapies (DMTs) for multiple sclerosis (MS) to the WHO Essential Medicine List (EML).

To address the feedback, we are planning a revised application to be submitted in 2022. We would like to outline in this letter our plans for the revised application for your comment and feedback. We are working closely both with the WHO Brain Health Unit and the WHO EML secretariat to ensure we can address all areas highlighted by the WHO Expert Committee.

Feedback 1: Need to review 'commonly used DMTs'.

We have noted the Committee's suggestion to consider two DMTs used off-label for MS; azathioprine and rituximab. These medicines have not been approved by regulatory authorities for the use in MS, but are used in clinical practice, in particular in low resource settings. As these drugs are off-label, we plan to review the existing evidence available and consider if these treatments should be recommended or not for multiple sclerosis, and under what conditions. We are working with a number of experts and stakeholders to ensure robustness and transparency of this process.

The Committee noted that "rituximab could have a relevant clinical role in treatment of MS, and recommended that any future application should include evidence for rituximab versus active comparators, not just placebo". We would like to highlight that there is only limited trial data for rituximab in MS. The pharmaceutical industry does not have incentives to run clinical trials with rituximab for MS, and we are therefore limited in our ability to address this issue. We will use the available evidence including observational, retrospective, and comparative effectiveness studies, previous reviews of the use of rituximab in MS and expert opinion. We will take the same approach with azathioprine. We hope this disciplined, but pragmatic approach is acceptable to the Committee.

All the MS DMTs with regulatory approval will be considered together with azathioprine and rituximab in the revised application.

Feedback 2: The superiority of presented medicines over other therapeutic options in the outcomes considered (benefits, harms, affordability) did not clearly emerge.

We would like to note that MS is a complex disease that requires a number of DMTs to be available in a health system to address different type, stage and activity of the disease, including specific sub-populations (e.g. paediatrics, pregnant individuals) and co-morbidities. The treatments have a range of efficacy and safety profiles that need to be carefully considered in individual treatment decisions. Given that the most efficacious treatments for MS come with greater risk and important contra-indications, the pathway to effective treatment at an individual level requires multiple options and an active treatment management system. Head-to-head comparison of the different DMTs are therefore complicated, and there are few clinical trials to address these questions.

Clear superiority, in terms of benefits and harms, of any medicine will therefore be an unlikely outcome of the revised application. It is important to point out that even though we will put forward a small number of specific DMTs, we believe all MS DMTs have a role to play in the treatment of MS. We will approach the revised application by laying out a framework to identify categories of DMTs that should be available to treat MS, as a minimum, in any health system.

We would therefore like to note that the DMTs mentioned by the Committee (e.g. natalizumab, dimethyl fumarate, cladribine) will be considered within this framework and not purely on their individual merits. The framework will emphasize the range of different types of DMTs needed. The specific medications put forward will act as a model approach.

We realise this tactic differs from other diseases areas and would welcome comment from the Committee.

Affordability of the different DMTs is a complex topic as drug prices are not publicly available or transparent. We will consider affordability within our framework, especially the medicines' patent status and availability of follow-on products. However, we would like to request that price alone would not be considered a barrier to be listed on the WHO EML. Once listed, a number of avenues to tackle availability and affordability of MS medicines can start through working with our key stakeholders and further developing our relationships with other international organisations such as the Clinton Health Access Initiative, who are willing to work with the WHO to improve drug access and delivery by resolving the various barriers that are impeding progress. The Medicines Patent Pool is interested to work closely with us to identify opportunities to use voluntary licensing for any patented small molecules for MS, particularly if they are added to the WHO EML.

Feedback 3: International MS guidelines

The Committee noted the "development in international MS guidelines and would welcome a revised application for EML inclusion in the future which considers the relative roles of all available medicines for MS". A number of widely recognised treatment guidelines for MS have been recently published. MSIF is planning to create resource-stratified guidelines in line with a successful EML application following 2023. We recognise that guidelines support EML listings, and are committed to use the categorised treatment baseline identified through the EML application to create practical guidance on treatment in different resource settings. These guidelines may take a regional approach to ensure they can easily be adopted or adapted to national settings.

We look forward to any additional comments and discussion with the WHO Expert Committee.

Best regards,

Peer Baneke, CEO of Multiple Sclerosis International Federation