June 2018

Agency/consultancy brief: Understanding the regulation and provision of multiple sclerosis disease modifying therapies in Latin America

Multiple Sclerosis International Federation (MSIF) is seeking the support of an agency or consultant to carry out a scoping exercise to increase our knowledge and understanding of the regulation and provision of multiple sclerosis (MS) treatments in the Latin America region. The work will be used by MSIF to develop a strategy to improve the regulation of disease modifying therapies (DMTs) in Latin America and improve access to information by people with MS and their healthcare professionals, ultimately to increase access to safe and effective DMTs in Latin America. For the purpose of this document 'treatments' refers to 'DMTs'.

Key words: Multiple sclerosis, Latin America, disease modifying therapies, biosimilar, medicines regulation

Background and context

The right treatment at the right time can help people with MS take control of their condition and live independently. However, it is critical that people with MS are prescribed safe and effective treatments that are made available based on suitable clinical evidence, with appropriate pharmacovigilance in place. Health is a human right and providing adequate services and treatment is essential to meeting this right.

There are a number of licensed, innovative DMTs available in Latin America. There are also a number of off-patent, repurposed, biosimilar and generic options in the pipeline or currently available. Provided that generics and biosimilars have the right clinical data to support their use, they can allow a health system to have access to treatments that are significantly cheaper.

Producing good quality biosimilars is more complex than producing generics due to the inherent properties of the biological drug. Biosimilars therefore require through bioequivalent studies, including clinical trials to demonstrate safety and efficacy. In Latin America, some biosimilars have not been fully assessed for their safety and efficacy, posing a potential risk that they are of poor quality. In some areas this is despite regulation dictating that these studies are required for approval.

There are a variety of complex regulatory systems in the region and the level of evidence for the different medicines is varied, as are the possible routes to assessing their safety and efficacy.

MS organisations in the region have a good overview of the DMTs currently being prescribed in their country. However, a lack of systematic data collection from official and reliable sources means the range of treatments, their safety and efficacy profiles, or who is prescribing which treatments and to whom is often unclear. Access to safe and effective medicine is an integral element of the right to health and governments' obligations to this effect. Despite having clear laws in this respect the reality of people with MS in Latin American countries is quite different.

The situation is driven by a number of factors, including: the significant cost of MS treatment; inconsistent or inadequate health insurance provision; health systems struggling to cope with demand; a variety of purchasing/procurement systems; a lack of medicine regulation or implementation of existing regulation; a lack of appropriate health technology assessment,

including for biosimilars; the existence of international and national pharmaceutical companies and poor patient engagement in regulatory decision-making.

Additionally, a variety of factors influence prescribing practice in the region, including the influence of medicine manufacturers, cost, licensing and reimbursement guidelines, prescribing guidelines, bulk purchases from external buyers that may not be regulated, and peer-to-peer guidance between healthcare professionals. Sometimes the brand of drug provided to the pwMS varies monthly (either due to non-specific prescribing or switching to available biosimilars by the pharmacy), which makes assessment of safety and efficacy, and pharmacovigilance difficult.

Patient choice in the region is also influenced by the (lack of) available DMTs and information available about the treatments, the safety and risk profile of a DMT, health insurance provision, and cost, access to overseas treatments or DMT and lifestyle factors.

Whilst these issues are particularly acute in Latin America, they are faced in a number of other areas of the world.

As a federation of MS organisations all united in our commitment to improve the lives of people affected by MS across the world, MSIF wants to better understand the scale of the problem in Latin America, with a view to using our collective influence to address it. We expect there to be lessons learnt and applied to our work elsewhere around the globe.

As part of MSIF's Strategy 2017–2021 to improve access to effective treatments and healthcare, our signposts of success include an increase in number of countries with reasonable access to treatment. With this work we want to increase **access to safe and effective DMTs in Latin America**.

To do this, over the coming years we will seek to:

- Improve the regulation of DMTs in Latin America
- Improve access to information about safe and effective DMTs for people with MS, healthcare professionals and MS organisations in the region

Task and objectives of the scoping exercise

As a first step, we want to improve our knowledge of the issues that exist in the region, their scale, the regulatory systems and identify the possible routes to influence change. The scoping exercise will help us to develop a strategy for tackling these issues. Given the diversity and complexity of the region, we wish to opt to focus on seven countries: Brazil, Argentina, Mexico, Paraguay, Guatemala, Costa Rica and Uruguay.

Through this scoping work, we therefore seek to:

- Better understand medicine regulation with regards to DMTs for MS, including:
    - What level of evidence is required by regulatory authorities for their assessment of biosimilar medicines. And, if a requirement to submit clinical evidence does exist, whether this is routinely implemented in practice.
    - What regulatory bodies exist, regulatory systems or bodies which are currently working well (good practice) and what regulations (national, regional or global) are followed (e.g. use WHO/FDA/EMA).
    - Which DMTs (innovator drugs and follow-on products) are currently approved, or prescribed despite not having been approved.
    - What region-wide health bodies exist and their role, e.g. Instituto Suramericano de Gobierno en Salud (South American Institute of Government in Health) and

Consejo Centro Americano de Ministerios de Salud (central American Council of Health Ministries).
    - The extent to which healthcare professionals and people affected by MS are engaged in the regulatory assessment of medicines.
    - The current pharmacovigilance systems in place and how effective they are.
    - A mapping of the prescribing pathway, and possible points at which inadequately tested or unregulated medicines might be substituted in.

- Better understand the influencers of prescribing practice in these countries, including:
    - The role and influence of the pharmaceutical industry (international and national).
    - What health insurance policies exist, and the DMTs available under these policies when applicable.
    - The role of professional bodies in setting standards for DMT prescribing.
    - The difference between prescribing practice in the private and public health systems.
      Other influencers on prescribing practice in the region/ by country (e.g. physicians not wanting to get involved and challenge the situation, lack of transparency, health insurance/pharmaceutical company relationships with decision-making body, national economic interests in local manufacturing vs global).

- Better understand the access points for advocacy and potential policy solutions to improve regulation of safe and effective DMTs, including:
    - Key opportunities to influence regulatory processes and structures in specific countries.
    - If any assessment of the impact of both good and poor medicine regulation in the region has been conducted, specific to MS or another long term condition. This includes any work to assess the impact on society, government or individuals.
    - 'Access to high cost treatment' regulation in law and how is the regulation implemented in practice.
    - Current coalitions or individual organisations working to improve medicine regulation and/or patient and public involvement, including those rooted in a human rights approach.
    - How influential international or regional bodies and associated guidance, such as the WHO/PAHO, EMA and FDA, are in the region.
    - Examples of successful influencing of the regulatory systems, preferably from the NGO sector.

Outputs

We expect this scoping work to include:
- A written report detailing the findings, including a literature review, outputs from focus groups or interviews with people affected by MS, interviews with healthcare professionals, experts and other stakeholders form the region.
- Recommendations for MSIF's collaborative work with organisations already working in the region.
- Recommendations as to the feasibility and appropriateness of an advocacy toolkit. If appropriate and feasible, recommendations as to how best to construct and develop a toolkit based on the findings of this scoping work.

MSIF support

MSIF and MS organisations in the region will provide relevant materials on the issue to the successful agency/consultant, and also facilitate liaison between the agency/consultant, relevant professionals and people with MS based in the region.

We would, in particular, expect the agency/consultant to work closely with MS organisations in the region to better understand the challenges they face in addressing the issue and how best international collaboration may support their work.

Methodology

We would expect the agency/consultant to consider methodology such as desk research, a review of evidence available, interviews with key stakeholders in the region and focus groups with people affected by MS, decision-makers, international and national pharmaceutical companies and prescribers. Information on conflict of interests should be included, e.g. funding from or investments in the different pharmaceutical companies.

The agency/consultant is expected to provide two updates by teleconference (sharing a draft report or relevant documents) to the working group to help guide the work. This will allow an opportunity for MSIF and member organisations to comment on progress made, emerging findings, and what this could mean for our work in the future.

Criteria for agency selection and how to apply

Please send the recruitment team:

1. Curriculum vitae of the person(s) working on the brief and/or details of your agency's experience, e.g. experience in medical regulatory system evaluation and public policy, experience working and liaising with regional and international organisations and patient organisations and language skills (English, Latin American Spanish and Portuguese if applicable). We welcome applications from around the world, but being based in Latin America would be an asset.
2. Cover letter and table below detailing how you would approach the brief. Please indicate what time-frame you would need for completing the work.
3. Two pieces of previous work that you/the agency has produced and written to demonstrate quality of writing.
4. Two references that we can contact.
5. Details around conflict of interest, please see below:

   "In order to avoid any conflict of interest, perceived or otherwise, agencies/consultant(s) should note that, in order to be eligible to tender for the work, they (or their company/agency/organisation) should ideally not have been employed by (as a permanent or temporary member of staff) or have carried out services for (in an advisory or consultancy capacity) national or international healthcare companies, or their subsidiaries, within the past 6 months. Consultants who have carried out services for national or international healthcare companies, or their subsidiaries, within the past 18 months, should declare this within their application."

Area	Role of agency	Proposed work	Experience	Timeframe and cost
Better understand medicine regulation with regards to DMTs for MS in seven countries	Desk research Review of evidence available Interviews/focus groups with key stakeholders in the region			
Better understand the influencers of prescribing practice in these countries	Desk research Interviews/focus groups			
Better understand the access points for advocacy and potential policy solutions to improve regulation of safe and effective DMTs	Desk research of international and national policy and its implementation Stakeholder mapping			
Involving people with MS				
Further questions to consider in formulation of our strategy				

Budget

Max £20,000 including travel and expenses

Timeline

Max six months, starting from August/September, please indicate expected timeframe needed.

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Appendices

Case study - Guatemala

In Guatemala, the DMTs covered by the Instituto Guatemalteco de Seguridad Social IGSS (social security) are: Interferon beta-1a (Avonex and Rebif), Interferon beta-1b (Betaferon) and Natalizumab (Tysabri), Teriflunomide (Aubagio) and Alemtuzumab (Lemtrada) and Fingolimod (Gilenya).

October 24, 2017: IGSS started the distribution of Blastoferón, a copy of Rebif. This product, made in Argentina, was chosen by UNOPS (The United Nations Office for Project Services), as part of an agreement with IGSS to buy medicines at a lower price. The basis of the auction did not differentiate originals, biosimilars or generic drugs.

November 3, 2017: a provisional "Amparo" was granted to ASOGEM. IGSS suspended the distribution of the copy and until now (March 2018), all the DMTs given to patients are the ones approved by FDA/EMA.

December 5, 2017: the Amparo was modified so that IGSS must provide eligible people with MS all the DMTs (not only Rebif) as was the situation until October 24, 2017.
January 28, 2018: The Constitutional Court denied the appeal made by IGSS regarding the provisional amparo.

Currently, we await the definitive resolution of the Amparo, the appeal from IGSS to this resolution and the acceptance or denial of the appeal from the Constitutional Court.
ASOGEM-Guatemala has undertaken a number of actions, including:

- Following up on the legal procedures
- Several meetings with IGSS to guarantee permanent supply of DMTs
- Providing information to people with MS and neurologists about FDA/EMA DMTs
- Hosting conferences about treatments in MS with neurologists and people with MS
- Investigating if the copy of Rebif (Blastoferón from Argentina) followed all the procedures to obtain the sanitary register to sell this product in Guatemala
- Raising concerns during a second bid handled by UNOPS, where the biosimilar was chosen again – ASOGEM reiterated that the amparo is in force

Glossary of terms

Term	Definition
Innovator drug or propietary medicines	The approved brand medicinal product also known as the reference product or proprietary medicine
Generic	Copy of a brand-name drug that is the same in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use
Biological	A medicinal product developed by 1 or more biotechnology practices such as recombinant DNA, controlled gene expression, or antibody technology.
Biosimilar	Biological medicinal product that is a new product claimed to be similar to an approved reference biologic, marketed by an independent entity subject to all applicable intellectual and marketing protection rights for the innovator product.
Bioequivalence	According to WHO two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailabilities, in terms of rate (Cmax and tmax) and extent of absorption (area under the curve), after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same.
Complex generic	Generic version of a complex molecular entity which includes both biosimilars and complex nonbiological drugs, which present similar issues.
Follow-on	A medicinal product that is intended to serve as a pharmaceutical and therapeutic equivalent to an already available agent.
Interchangeable	Interchangeable is a higher standard than equivalent. It indicates that the generic drug is expected to produce the same clinical result as the reference product in an individual patient.
Shelf life	Time interval during which a drug product is expected to remain within the approved specification provided that it is stored under the conditions defined on the label and in the proposed container and closure.
Pharmacovigilance	The practice of monitoring the effects of medical drugs after they have been licensed for use.

Further background information

MS is a chronic, degenerative autoimmune inflammatory disease of the central nervous system. MS remains a complex condition that is likely caused by the interplay of still unknown genetic and environmental factors. MS is different for everyone and you can get symptoms in many parts of your body. Common symptoms include pain, fatigue, balance problems and muscle spasms and stiffness.

The prevalence of MS is different in every continent, changing according to geographical and environmental characteristics. The areas with the highest prevalence in the world are Europe and North America. In Latin America, the prevalence is higher in areas where there is greater European migration, as in the case of Argentina, Chile, Brazil, Uruguay and Mexico, and there have been no identified cases amongst native Indian populations. Environmental factors may influence the prevalence of MS in Latin America, and it seems as if there are protective factors such as exposure to ultraviolet radiation and the presence of parasitosis. The estimated number of people diagnosed with MS in Latin America is approximately 50,000 (although this is questioned). MS is considered a rare condition.

Latin America is a large and diverse continent. It has a variable and wide-ranging climate, from tropical to sub-Antarctic. There are a number of languages, including Spanish, Portuguese, English, French, Dutch, indigenous dialects and others. Each country has its own regulatory system for medicines.

There are a number of different types of MS, and most people are initially diagnosed with a relapsing form of the condition. Disease Modifying Therapies (DMTs) help to stop relapses and slow progression in relapsing forms of MS.

DMTs

There are a number of licensed, innovative DMTs available. There are also a number of off-patent, repurposed, biosimilar and generic options in the pipeline or available currently – the level of evidence for these different medicines is varied, as are the possible routes to assessing their safety and efficacy.

The US Food and Drug Administration (FDA) have approved the following DMTs for MS as they have been found through clinical trials to reduce the number of relapses, delay progression of disability, and limit new disease activity. The European Medicines Agency (EMA) has also approved all of the drugs below apart from mitoxantrone.

- Injectable medications
  - Avonex (interferon beta-1a)
  - Betaseron (interferon beta-1b)
  - Copaxone (glatiramer acetate)
  - Extavia (interferon beta-1b)
  - Glatiramer Acetate Injection (glatiramer acetate -- generic equivalent of Copaxone 20 mg and 40 mg doses)
  - Glatopa (glatiramer acetate -- generic equivalent of Copaxone 20mg dose)
  - Plegridy (peginterferon beta-1a)
  - Rebif (interferon beta-1a)
- Oral medications
  - Aubagio (teriflunomide)
  - Gilenya (fingolimod)
  - Tecfidera (dimethyl fumarate)
  - Mavenclad (cladribine)

- Infused medications
  - Lemtrada (alemtuzumab)
  - Novantrone (mitoxantrone)
  - Ocrevus (ocrelizumab)
  - Tysabri (natalizumab)