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Specific Aspects of Immunotherapy for Multiple Sclerosis in Switzerland—A Structured Commentary, Update 2022

Christoph Friedli [1], Anke Salmen [1], Robert Hoepner [1], Lutz Achtnichts [2], Sandra Bigi [3,4], Tobias Derfuss [5], Claudio Gobbi [6,7], Nicole Kamber [1], Christian P. Kamm [1,8], Jens Kuhle [5], Patrice Lalive [9,10,11], Stefanie Müller [12], Athina Papadopoulou [5], Caroline Pot [13], Chiara Zecca [6,7] and Andrew Chan [1,*] on behalf of the Scientific Advisory Board of the Swiss Multiple Sclerosis Society and the Swiss Neurological Society

1 Department of Neurology, Inselspital, Bern University Hospital and University of Bern, 3010 Bern, Switzerland
2 Department of Neurology, Aarau Cantonal Hospital, 5000 Aarau, Switzerland
3 Institute of Social and Preventive Medicine, University of Bern, 3010 Bern, Switzerland
4 Division of Pediatric Neurology, Department of Pediatrics, Children's Hospital Lucerne, 6000 Lucerne, Switzerland
5 Neurologic Clinic and Policlinic and Research Center for Clinical Neuroimmunology and Neuroscience, Departments of Medicine, Biomedicine, and Clinical Research, University Hospital Basel, University of Basel, 4031 Basel, Switzerland
6 Multiple Sclerosis Center, Neurocenter of Southern Switzerland, EOC, 6900 Lugano, Switzerland
7 Faculty of Biomedical Sciences, Università della Svizzera Italiana, 6900 Lugano, Switzerland
8 Neurocentre, Luzerner Kantonsspital, Spitalstrasse, 6000 Luzern, Switzerland
9 Division of Neurology, Department of Clinical Neurosciences, Geneva University Hospitals and Faculty of Medicine, University of Geneva, 1211 Geneva, Switzerland
10 Division of Laboratory Medicine, Diagnostic Department, Geneva University Hospital, 1211 Geneva, Switzerland
11 Department of Pathology and Immunology, Faculty of Medicine, University of Geneva, 1211 Geneva, Switzerland
12 Department of Neurology, Cantonal Hospital St Gallen, 9000 St Gallen, Switzerland
13 Service of Neurology, Department of Clinical Neurosciences, Lausanne University Hospital, University of Lausanne, 1011 Lausanne, Switzerland
* Correspondence: andrew.chan@insel.ch

Abstract: Multiple sclerosis (MS), particularly relapsing MS (RMS), has become a treatable disease in recent decades, and immunotherapies are now able to influence long-term disease course. A wide range of disease-modifying drugs are available, which makes the choice of therapy in individual cases considerably more complex. Due to specific regulatory aspects (partly diverging approvals by Swissmedic compared to the European Medicines Agency (EMA), and an independent evaluation process for the Federal Office of Public Health (FOPH) specialities list (SL)), we issued a consensus recommendation regarding specific aspects of immunotherapy for MS in Switzerland in 2019. Here, we present revised recommendations with an update on newly approved drugs and new safety aspects, also in reference to the risk of COVID-19 infection and vaccination.

Keywords: multiple sclerosis; immunotherapy

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1. Introduction

In recent years, the number of available disease-modifying therapies for multiple sclerosis (MS) has continued to increase. In addition to new therapies for relapsing forms of the disease, a novel treatment option has been approved for secondary-progressive multiple sclerosis (SPMS). The individual choice of drugs, even in routine situations such as a treatment after an initial clinical manifestation of MS, is therefore becoming increasingly complex. Moreover, changes in therapy caused by factors of efficacy or safety are more

difficult to manage as a number of pharmacological factors (mechanisms of action, pharmacokinetics, interactions/"wash out") and individual factors (e.g., age/'immunosenescence', comorbidities, risk of infections, pregnancy) have to be considered from a risk/benefit perspective for each individual person with MS (pwMS). Different assessments of risk/benefit profiles are reflected in the drug approvals, which can markedly differ depending on the area of market approval. This is particularly important for Switzerland, as there are sometimes considerable differences in approval (e.g., "first-line" vs. "second-line" treatments) compared with neighbouring countries (EMA approval area). Another specific aspect in Switzerland is the independent cost–benefit evaluation by the FOPH, which regulates inclusion in the SL as the basis of reimbursement for compulsory health insurance. For these reasons, a group of authors mandated by the Swiss Multiple Sclerosis Society and Swiss Neurological Society already published a commentary in 2019 [1,2]. Its aim was to provide specific recommendations on immunotherapies for MS, for which there are specific approvals, safety regulations or SL restrictions in Switzerland. Here, we present an update of newly approved medications, taking into consideration the changing environment caused by the COVID-19 (coronavirus disease 2019) pandemic with regard to infection risk and vaccination recommendations for pwMS.

2. Methodology

Our methodology is based on the original version of the 2019 structured commentary [1,2]. After this manuscript was drafted by a core group of authors (CF, AS, AC), it was reviewed by the Swiss MS Society (SMSS) 'Immunotherapies' working group before final acceptance from the authors.

The process of preparing this structured commentary was actively supported by all named individuals, responsible representatives of organisations (SMSS and Swiss Neurological Society (SNS)), and the commentaries and recommendations made correspond to a consensus between these groups but without following formalised criteria (e.g., Delphi method). Hence, this structured commentary does not follow the formal requirements of a guideline.

In addition to the specified literature, the commentary on individual drugs was based on current product information from Swissmedic and the EMA, as well as the SL of the FOPH. No wider systematic literature review has been previously conducted. We discuss disease-modifying drugs approved since 2019 and briefly highlight new safety aspects of selected disease-modifying drugs. We do not describe symptomatic therapies. Specific recommendations regarding pregnancy/family planning will follow in a separate commentary (Graber, Chan, in preparation).

This commentary is structured as follows:

- Name/trade name of the drug;
- Comparative list of indications according to the Swiss product information, the SL published by the FOPH, or the indication according to the EMA ('*Summary of Product Characteristics*' [SmPC], usually in reference to Section 5.1, which briefly describes the pivotal studies);
- Considerations of patient selection;
- Considerations of selected safety aspects;
- Considerations of the confirmation of cost coverage (if applicable).

We do not outline all safety aspects of immunotherapies in our manuscript, highlighting only selected aspects that seem particularly important. For a full outline of safety aspects we refer to the respective Swiss product information [3].

3. Commentary on the Different Disease Courses and Activity of Multiple Sclerosis

Current drug approvals refer to different disease courses and activity. Pathophysiologically multiple sclerosis is currently considered a continuum with acute, focal inflammatory lesions, and spatially compartmentalised chronic inflammation within the CNS; neurodegenerative/neuroregenerative processes may also contribute [4,5]. The extent of the different processes can vary both inter- and intra-individually and over time [5]. Thus, from a pathophysiological point of view, the conceptual dichotomy of relapsing vs. progressive is controversial since underlying mechanisms may at least partly overlap. This may already be clinically reflected in observations in early stages of the disease, such as progression independent of relapse activity (PIRA) [6]. However, thus far there are no unequivocal biomarkers to objectively and accurately capture progressive disease worsening, aside from clinical assessment with the Expanded Disability Status Scale (EDSS) or other less well-established clinical measures [7].

Current classification criteria take pathophysiological aspects into account by considering modifiers for the underlying course of the disease [8]. Thus, for each patient two factors should be determined: (a) evidence of activity; and (b) evidence of progression. Signs of activity may include clinical relapses, as well as imaging markers (new/enlarging T2 or FLAIR lesions and/or contrast-enhancing lesions in the MRI examination). The evaluation of whether progression is present should be primarily clinical with at least annual neurological examinations.

While early therapeutic intervention is also desirable in progressive forms, determination of progression can only be confirmed post hoc. There are no generally accepted diagnostic criteria, particularly for secondary-progressive multiple sclerosis, which also complicates stratification in clinical studies [9]. Thus far, no further clinical or marker-based algorithms for differentiating progressive forms have been established, partly due to methodological difficulties and a lack of validation [10].

Although the approval of several medications is related to MS disease activity, there is currently no unifying definition of MS disease activity. This is also reflected by different descriptions in Swiss product information [3], and the SL, respectively [11]. Thus, 'highly active' RRMS for therapy with alemtuzumab is not further detailed in the Swiss product information and the SL, whereas for therapy with natalizumab it is defined as [3,11]: 'Patients with high disease activity despite treatment with a complete and appropriate cycle of at least one disease-modifying therapy or patients with rapidly progressive RRMS, defined by 2 or more disabling relapses in a year and with 1 or more gadolinium-enhancing lesions on a brain MRI scan or with a significant increase in T2 lesions compared with a recent MRI.' Furthermore, disease activity requirements in product information and the SL do not necessarily correspond to pivotal studies. It is essential to note that no generally accepted definition of the term "highly active" exists and that assessment depends on the individual situation. Therefore, this is a judgment call subject to appropriate assessment of individual cases carried out by the treating physician [1]. Individual assessment should also consider paraclinical parameters relevant for prognosis, in addition to the clinical dynamics of the disease (Table 1). Factors such as the impact of the disease on one's profession, hobbies, family planning, life situation, etc., should also be taken into consideration in the overall assessment of the activity and severity of the disease course. This view is also in line with the recommendations of corresponding European guidelines (EAN/ECTRIMS), which consider highly efficient therapies early in the disease course depending on clinical, imaging and patient-specific factors [12].

Table 1. Negative prognostic factors for multiple sclerosis (adapted according to [13–20]).

Negative Prognostic Factors for Multiple Sclerosis				
Clinical	**Demographic**	**Biochemical**	**Imaging**	**Electrophysiological**
High relapse rate	Older age at disease onset	CSF specific OCB	Number and volume of 'black holes' *	Pathological MEP
Incomplete recovery from relapses	Male	Intrathecal IgM synthesis	Number, volume and location of T2 lesions	
EDSS progression	Non-white ethnicity		Contrast-enhancing lesions	
Efferent symptoms/signs			Number of intracortical lesions in DIR sequence	
Higher BMI			Lower brain volume (WBV, WM, GM, spinal)	
Longer disease duration			Spinal lesions at initial diagnosis	
Smoker			Pathological OCT	
No immunotherapy				

Abbreviations: BMI: body mass index; DIR: double inversion recovery; EDSS: expanded disability status scale; GM: grey matter; IgM: Immunoglobulin M; MEP: motor evoked potential; OCB: oligoclonal bands; OCT: optical coherence tomography; WBV: whole brain volume; WM: white matter * black holes: T1-hypointense lesions as markers of axonal loss and neuronal destruction.

4. Commentary on COVID-19 and Varizella Zoster vaccination

4.1. Impact of Disease-Modifying Therapies on COVID-19 Infection

The ongoing pandemic has specific implications for the immunotherapy of MS. Various studies show an increased risk of severe COVID-19 infection in pwMS treated with anti-CD20 therapies and methylprednisolone therapy within the last month, as well as an increased mortality in pwMS treated with anti-CD20 therapies [21–23]. A meta-analysis [22] of more than 4000 pwMS with COVID-19 showed the highest hospitalisation and mortality rates in those not receiving disease-modifying therapy (42.9% and 8.4%, respectively), followed by pwMS on B-cell-depleting therapies (29.2% and 2.5%, respectively). It should be noted that pwMS not receiving disease-modifying therapy had more risk factors independent of MS (older age; more co-morbidities). MS is not a major risk factor for severe COVID-19 per se; however, there is increasing evidence that more severe COVID-19 is observed in pwMS, particularly in the presence of additional risk factors such as old age, obesity, hypertension, cardiovascular diseases, diabetes, and higher-grade disability [24]. Current evidence shows that pregnant women without MS suffering from COVID-19 have an increased risk of intensive care unit admission, extracorporeal membranous oxygenation requirement, preterm birth, and perinatal death [25]. Additionally, in pregnant pwMS with COVID-19, an increased risk of preterm birth and intensive care unit admission was observed, whereas data on fetal outcomes remain limited [26].

4.2. Impact of MS Therapies on COVID Vaccines

Studies on pwMS found no specific adverse reactions to the Pfizer/BioN Tech (Comirnaty®) and Moderna (Spikevax®) mRNA vaccines available in Switzerland, whereas MS-specific studies for the vector-based vaccine of Janssen (COVID-19 Vaccine Janssen®) and the Novavax protein vaccine (Nuvaxovid®) are lacking [27,28]. When interpreting vaccination data for pwMS on immunotherapies, it is important to point out differences in humoral (antibody-associated) or cellular immune responses, which collectively determine clinical effects and vaccine protection. In addition, it should also be noted that no 'vaccination titre' was defined as of December 2022 that is considered to be reliably protective. There is increasing evidence of a reduced humoral immune response in pwMS on immunotherapy with ocrelizumab and fingolimod (also with reduced T-cell response with fingolimod) [27,29,30]. A further study from Switzerland confirmed a reduced humoral and cellular immune response to COVID-19 vaccines in patients with different clinical diagnoses on anti-CD20 therapies [23,31,32]. However, other studies show intact cellular immune responses both with B-cell-depleting therapies and the S1P receptor modulator

siponimod [27,28,33–36]. The first clinical studies suggested that the risk of breakthrough SARS-CoV-2 infections is mainly associated with reduced levels of the virus-specific humoral immune response; however, further developments must be monitored [37]. On 23 May 2022, the FOPH issued an updated vaccination recommendation stating that three doses (each 4 weeks apart) of the same mRNA vaccine should be administered to pwMS on 'severely immunosuppressive therapy' for their basic immunisation, irrespective of antibody titres. In those pwMS, a fourth (4 months after the third vaccination) and a fifth (4 months after the fourth vaccination, as an off-label treatment) mRNA booster vaccination is recommended [38]. In this context, the SMSS defined therapies with sphingosine-1-phosphate receptor modulators (S1PRM, fingolimod, ozanimod, ponesimod, siponimod) and anti CD20 antibodies (rituximab, ocrelizumab, ofatumumab) as 'severely immunosuppressive therapy' [39]. Regarding vaccine recommendations, we also refer to the homepage of the SMSS, where this group of authors periodically publish updates [39]. We recommend that pwMS on 'severely immunosuppressive therapies' (see above) follow appropriate safety measures (including hygiene measures, masks, distancing rules), and point out that contact people can help to protect pwMS by having a vaccination.

4.3. General Recommendation for Varicella Zoster Vaccination

The establishment of immunity, including vaccination against VZV, is recommended in pwMS under treatments with an increased risk of zoster infections, such as monoclonal antibodies, S1PRM, cladribine and fumarates (in case of lymphopenia). As vaccination with live vaccines is contraindicated for pwMS with immunotherapies, vaccination with the VZV glycoprotein E vaccine Shingrix® [40], which was recently approved (February 2022) in Switzerland, can be used in pwMS. Shingrix® is authorised for the prevention of herpes zoster in adults aged 50 years and older, and in adults aged 18 years and older at increased risk of herpes zoster.

5. Commentary on Individual Drugs

In the following section, we describe the factors deemed to be particularly significant for Swiss physicians. Although some safety aspects are highlighted, we do not provide a complete summary and refer to the respective product information [3,11].

Drugs approved since last commentary in 2019.

Diroximel fumarate (Vumerity®) indication information Table 2.

Table 2. Diroximel fumarate (Vumerity®), approval CH 11/21.

Indication According to Swiss Product Information [3]	*Indication According to the SL* [11]	*Indication According to EMA Product Information* [41]
'Vumerity® is indicated for the treatment of patients with relapsing–remitting multiple sclerosis (MS) to reduce the frequency of relapses.'	No restriction.	'Vumerity® is indicated for the treatment of adult patients with relapsing–remitting multiple sclerosis (see Section 5.1). Vumerity® should be administered under the supervision of a doctor experienced in treating multiple sclerosis.'

5.1. Commentary

5.1.1. Considerations of Patient Selection

In Switzerland and the EMA area, diroximel fumarate (DRF) is approved as an oral therapy for patients with relapsing–remitting multiple sclerosis. DRF has been developed with the aim of improving gastrointestinal tolerability. DRF is quickly metabolised to monomethyl fumarate (MMF), which is the primary metabolite of dimethyl fumarate (DMF, Tecfidera®); thus, similar effects of DRF and DMF on the pathophysiology of MS are postulated [3,42,43]. However, no efficacy study of higher evidence was conducted for DRF. Bioequivalence in systemic exposure to MMF after the administration of 462 mg DRF and 240 mg DMF has been shown [42,43]. According to Swiss law, bioequivalence exists if the

drug level of the generic product is between 80–125% of the original drug [44]. Two phase III safety/tolerability studies were conducted on diroximel fumarate: EVOLVE-MS-1 [43], an ongoing 2-year safety study, and EVOLVE-MS-2 [42], a randomised double-blind study comparing the gastrointestinal tolerability of diroximel fumarate to dimethyl fumarate. Based on the benefit–risk profile, diroximel fumarate can be used as a drug for first-line therapy in Switzerland without specific activity criteria.

5.1.2. Considerations of Selected Safety Aspects

In current clinical trials [42,43], the safety profile observed in pwMS treated with DRF was similar to clinical trial experience with DMF. However, pwMS treated with DRF experienced 46% fewer gastrointestinal side effects, and discontinuation due to gastrointestinal side effects was less frequent (0.8% vs. 4.8%). At present, no cases of progressive multifocal leukoencephalopathy (PML) have been described with diroximel fumarate; however, as with dimethyl fumarate, prolonged and severe lymphopenia should be avoided. Prolonged moderate (<0.8–0.5 G/L over 6 months) lymphopenia was observed in 7.3% of pwMS taking DRF, while no prolonged severe (<0.5 G/L over 6 months) lymphopenia was observed, and as of now, lymphopenia has not been linked with opportunistic infections. Flushing was observed in 32.8% of the study population compared to 40.6% taking DMF [42] but was seldom the reason for treatment discontinuation (<1%) [45].

Ofatumumab (Kesimpta®) indication information Table 3.

Table 3. Ofatumumab (Kesimpta®), approval CH 04/21.

Indication According to Swiss Product Information [3]	*Indication According to the SL* [11]	*Indication According to EMA Product Information* [41]	*Inclusion Criteria and Main Findings of Phase III Studies* [46]
'Kesimpta® is indicated for the treatment of adult patients with active relapsing forms of multiple sclerosis (MS).'	'For the treatment of adult patients with active relapsing forms of multiple sclerosis (MS).'	'Kesimpta® is indicated for the treatment of adult patients with relapsing multiple sclerosis with disease activity, defined by clinical findings or imaging (see Section 5.1).'	• age 18–55 years • active RMS: at least one relapse in the last year, or two relapses in the last two years combined with MRI evidence of a contrast-enhancing lesion in the last year. • EDSS score 0–5.5 • Active comparator: teriflunomide • Baseline characteristics1′882 pwMS (mean age 38 y, 2/3 female, mean EDSS 3.0, 40% therapy naïve, mean number of relapses 1.2 in last 12 months, SPMS 5.7%) • Primary endpoint: ARR: ofatumumab 0.10–0.11 vs. teriflunomide 0.22–0.25, $p < 0.001$ • CDP at 3 months: ofatumumab 10.9% vs. teriflunomide 15.0%, $p = 0.002$ • Gd-enhancing lesions: ofatumumab 0.01–0.03 vs. teriflunomide 0.45–0.51, $p < 0.001$ • New/enlarging T2 lesions: ofatumumab 0.64–0.72 vs. teriflunomide 4.00–4.15, $p < 0.001$ • Annual rate of brain-volume loss: no significant difference, ofatumumab −0.28–−0.29 vs. teriflunomide −0.35, $p = 0.12–0.13$

Abbreviations: ARR: annual relapse rate; CDP: confirmed disability progression; EDSS: expanded disability status scale; MRI: magnetic resonance imaging; pwMS: people with Multiple Sclerosis; RMS: relapsing Multiple Sclerosis; SPMS: secondary progressive Multiple Sclerosis; y: years.

5.2. Commentary

5.2.1. Considerations of Patient Selection

In Switzerland and the EMA area, ofatumumab is approved for patients with relapsing MS with signs of disease activity. Whereas the Swiss approval does not specify disease activity, the EMA approval refers to Section 5.1 of the summary of product characteristics (SmPC), with specific and quantified clinical and MRI criteria based on the inclusion criteria of the pivotal studies [46]. Thus, the Swissmedic approval gives the treating physician more freedom in the indication. Considering the study results with the active comparator teriflunomide, the authors consider ofatumumab as a first- or second-line therapy, taking into account disease activity as well as individual prognostic risk factors and safety considerations.

5.2.2. Considerations of Selected Safety Aspects

Ofatumumab is a fully human anti-CD20 antibody (IgG1). Compared to ocrelizumab and rituximab, the binding epitope differs, resulting in comparably greater complement-dependent cytotoxicity (CDC) [47] and antibody-dependent cell-mediated cytotoxicity (ADCC) to a lesser extent. It is hypothesised that this will allow for lower dosing compared to other anti-CD20 therapies [48].

In the pivotal studies [46], the subcutaneous administration of ofatumumab resulted in a rapid and sustained reduction in B cells as early as two weeks after treatment initiation. After discontinuation, B cells returned to normal levels in at least 50% of pwMS within 24 to 36 weeks. To date, there have been no cases of PML reported in the clinical study programme or in the post-marketing pharmacovigilance of ofatumumab in MS. However, fatal cases of PML occurred in patients who were treated with ofatumumab for chronic lymphocytic leukaemia (Azerra®), at significantly higher and intravenous doses than those recommended for MS treatment but for a shorter treatment duration. In addition, the risk of carry-over PML must also be considered when switching immunotherapy to ofatumumab. Thus, a high vigilance for the detection of PML is also warranted during treatment with ofatumumab, and appropriate safety measures (MRI and CSF) need to be followed, especially during switching [1,2]. As hepatitis B reactivation can occur with anti-CD20 antibodies, pwMS with active hepatitis B disease should not be treated; in addition, all pwMS must be screened for hepatitis B virus (HBV) before initiating treatment (HBsAg and Anti-HBc) [49]. In individual cases and in consultation with a hepatologist, a treatment with an anti-CD20 therapy can be evaluated despite a positive hepatitis B serology in the absence of florid infection [50], and a prophylactic antiviral therapy should be evaluated.

We recommend an update of vaccine status and an evaluation of differential blood counts, lymphocyte subpopulations, and immunoglobulin values prior to the initiation of an anti-CD20 therapy and at least every six months during therapy. In pivotal studies on RMS [46], a decrease in mean IgM (but not IgG) was observed during the observation period of up to 120 weeks. This was not associated with an increased risk of (severe) infections, at least over this relatively short period. Control of immunoglobulin levels during anti-CD20 therapy is reasonable since long-term therapy can lead to a gradual decrease. Up to 15% of DMT-treated and untreated pwMS show an immunoglobulin G deficiency [51].

Ozanimod (Zeposia®) indication information Table 4.

Table 4. Ozanimod (Zeposia®), approval CH 10/2020.

Indication According to Swiss Product Information [3]	*Indication According to the SL* [11]	*Indication According to EMA Product Information* [41]	*Inclusion Criteria and Main Findings of Phase III Studies* [52,53]
'Zeposia® is indicated for the treatment of adult patients with relapsing–remitting multiple sclerosis (MS).'	'Treatment of relapsing–remitting multiple sclerosis (MS). Initial prescription by the Swiss Medical Association (FMH) consultant for neurology.'	'Zeposia® is indicated for the treatment of adult patients with relapsing–remitting multiple sclerosis (RRMS) with inflammatory disease activity as demonstrated by clinical findings or imaging.'	• age 18–55 years • RMS with relapse in last 12 months or last 24 months with CEL in last 12 months • EDSS score 0–5.0 • Active comparator: interferon beta-1a i.m. • Baseline characteristics: 2′666 pwMS (mean age 34–36 y, mean EDSS 2.5–2.7, 2/3 therapy naïve, mean number of relapses 1.3–1.4 in last 12 months, SPMS 0.2–0.7%) • Primary endpoints: Relative reduction in adjusted ARR through month 12 with ozanimod of rate ratio 0.52–0.69, $p < 0.0001$; relative reduction in adjusted ARR through month 24 with ozanimod of rate ratio 0.62–0.79, $p < 0.0001$ • Mean number of new/enlarging T2 lesions per scan over 12 months (absolute value): ozanimod 1.47–2.14 vs. IFNB1a 2.84, $p < 0.0001$; Mean number of new/enlarging T2 lesions per scan over 24 months (absolute value): ozanimod 1.84–2.09 vs. IFNB1a 3.18, $p < 0.0001$ • Mean number of gd-enhancing lesions at month 12: ozanimod 0.16–0.29 vs. IFNB1a 0.43, $p < 0.0001$; Mean number of gd-enhancing lesions at month 24: ozanimod 0.18–0.20 vs. IFNB1a 0.37, $p = 0.0006$ • CDP at 3 months: ozanimod 6.5–7.6% vs. IFNB1a 7.8, $p = 0.7651$ • Whole brain volume (mean percentage change from baseline to month 12): ozanimod −0.41–−0.49 vs. IFNB1a −0.61, $p < 0.0001$

Abbreviations: ARR: annual relapse rate; CDP: confirmed disability progression; EDSS: expanded disability status scale; gd: gadolinium; IFNB1a: interferon-beta-1a; i.m.: intramuscular; MRI: magnetic resonance imaging; pwMS: people with Multiple Sclerosis; RMS: relapsing Multiple Sclerosis; SPMS: secondary progressive Multiple Sclerosis; y: years.

5.3. Commentary

5.3.1. Considerations of Patient Selection

EMA requires signs of disease activity (clinical or MRI), whereas Swissmedic approval does not mention this criterion. Considering the study data with the active comparator interferon-beta 1a i.m., individual prognostic factors, and safety considerations, the authors consider the use of ozanimod as a first- and second-line therapy as justified.

5.3.2. Considerations of Selected Safety Aspects

Ozanimod is a selective S1PRM of S1PR1 and S1PR5 [54].

In pwMS treated with ozanimod, one PML case has been described so far [55]. Upon discontinuation, the possibility of a clinical worsening with "rebound" activity, as reported for fingolimod should be considered, although this has not yet been reported after discontinuation of ozanimod. The first data presented in abstract form show relapses in 2.3% of pwMS after the discontinuation of ozanimod, reported as mild or moderate by the investigators, and 70% of pwMS with a relapse showed a full recovery within 30 days [56]. Whether different pharmacodynamic or -kinetic characteristics (e.g., metabolites with a

comparatively long half-life) influence the rebound risk is unclear. It should be noted that a combination of ozanimod with certain co-medications, such as breast cancer resistance protein (BCRP) inhibitors (e.g., ciclosporin), MAO inhibitors (e.g., selegiline) or rifampicin is not recommended [3]. The concomitant use of ozanimod and strong CYP2C8 inhibitors (e.g., clopidogrel) warrants caution. One case of PML has been reported under ozanimod [55].

Ponesimod (Ponvory®) indication information Table 5.

Table 5. Ponesimod (Ponvory®), approval CH 11/21.

Indication According to Swiss Product Information [3]	*Indication According to the SL* [11]	*Indication According to EMA Product Information* [41]	*Inclusion Criteria and Main Findings of Phase III Study* [57]
'Ponvory® is indicated for the treatment of adult patients with relapsing–remitting forms of multiple sclerosis (RRMS) with active disease that is defined by clinical or imaging features.'	Temporary limitation until 31.12.2024: Treatment of relapsing–remitting multiple sclerosis (MS). Initial prescription by the Swiss Medical Association (FMH) consultant for neurology.	'Ponvory® is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis with active disease which is defined by clinical or imaging features.'	• age 18–55 years • RMS with ≥1 relapses in last 12 month, or ≥2 relapses in last 24 months, or ≥1 CEL on MRI within last 6 months • EDSS score 0–5.5 • Active comparator: teriflunomide • Baseline characteristics: 1'133 pwMS (mean age 37 y, mean EDSS 2.6, 2/3 therapy naïve, mean number of relapses 1.2–1.3 in last 12 months, SPMS 2.5–2.6%) • Primary endpoint: ARR: reduction of 30.5% with ponesimod, $p < 0.001$ • LS mean FSIQ-RMS weekly symptoms score change (95% CL): ponesimod −0.01 vs. teriflunomide 3.56, $p = 0.002$ • Mean cumulative combined unique active lesions */y (95% CL): ponesimod 1.405 vs. teriflunomide 3.164, $p < 0.0001$ • Patients with first CDP at 3 months: ponesimod 10.1% vs. teriflunomide 12.4%, $p = 0.29$ • LS mean change in brain volume: ponesimod −0.91% vs. teriflunomide −1.25, $p = 0.001$

Abbreviations: ARR: annual relapse rate; CEL: contrast enhancing lesions; EDSS: expanded disability status scale; FSIQ-RMS: fatigue symptom and impact questionnaire-relapsing multiple sclerosis; LS: least squares; MRI: magnetic resonance imaging; pwMS: people with Multiple Sclerosis; RMS: relapsing Multiple Sclerosis; SPMS: secondary progressive Multiple Sclerosis; y: years; 95% CL: 95% confidence limit, * combined unique active lesions: new Gd+ T1 lesions or new or enlarging T2 lesions (without double counting of lesions).

5.4. Commentary

5.4.1. Considerations of Patient Selection

Ponesimod is approved in Switzerland for patients with relapsing–remitting forms of multiple sclerosis only, whereas in the EMA area it is approved for relapsing forms. Both in Switzerland and the EMA area, signs of active disease defined by clinical or imaging features are required. In a phase III study, ponesimod demonstrated efficacy against fatigue as a secondary outcome parameter [57]. However, the fatigue scale used is novel, and thus clinical impact needs to be validated. In addition, it is unclear if this effect is unique to ponesimod. In our view, considering data with the active comparator teriflunomide, individual prognostic factors, and safety considerations, the use of ponesimod as both a first- and second-line therapy is justified.

5.4.2. Considerations of Selected Safety Aspects

Ponesimod exhibits a high specificity for S1P1 receptors, however, it is currently unclear if this has any specific clinical implications. Thus far, no cases of PML have been reported in phase III studies of ponesimod during 108 weeks.

Upon discontinuation of this therapy, the possibility of increased disease activity ("rebound") must be considered, as with other S1P receptor modulators and in light of the short T1/2 of ponesimod, despite there being no data on this phenomenon with ponesimod.

Siponimod (Mayzent®) indication information Table 6.

Table 6. Siponimod (Mayzent®), approval CH 01/2021.

Indication According to Swiss Product Information [3]	*Indication According to the SL* [11]	*Indication According to EMA Product Information* [41]	*Inclusion Criteria and Main Findings of Phase III Study* [58] *and Sub-Group Analysis* [59]
'Mayzent® is used to treat adults patients with secondary-progressive multiple sclerosis (SPMS) with inflammatory disease activity, as evidenced by clinical relapses or imaging.'	'Mayzent® is used to treat adults patients with secondary-progressive multiple sclerosis (SPMS) with inflammatory disease activity, as evidenced by clinical relapses or imaging.'	'Mayzent® is indicated for the treatment of adults with secondary-progressive multiple sclerosis with disease activity as evidenced by relapses or imaging signs of inflammatory activity (see Section 5.1).'	• age 18–60 years • SPMS • EDSS score 3.0–6.5 • Placebo controlled • Baseline characteristics: 1′651 pwMS (mean age 48 y, mean EDSS 5.4, 1/5 therapy naïve, mean number of relapses 0.2–0.3 in last 12 months, mean disease duration 16.8 y, median time since SPMS conversion 3.8 y) were included • 47.3% with clinical or imaging disease activity in last 24 months • Primary endpoint: CDP at 3 months: siponimod 26% vs. 32% placebo, $p = 0.013$ • CDP at 6 months: siponimod 20% vs. placebo 26%, $p = 0.0058$ • ARR: siponimod 0.07 vs. 0.16 placebo, $p < 0.0001$ • Number of gd-enhancing lesions: siponimod 0.08 vs. placebo 0.60, $p < 0.0001$ • Mean number of new/enlarging T2 lesions: siponimod 0.70 vs. placebo 3.60, $p < 0.0001$ • Brain volume change from baseline (month 12, adjusted mean): siponimod −0.28% vs. placebo −0.46%, $p < 0.0001$. * Post-hoc sub-group analysis of patients with clinical or imaging disease activity in last 24 months: HR reduction in CDP after 3 and 6 months by 31% ($p = 0.0094$) and 37% ($p = 0.0040$)

Abbreviations: ARR: annual relapse rate; CDP: confirmed disability progression; EDSS: expanded disability status scale; gd: gadolinium; HR: hazard ratio; MRI: magnetic resonance imaging; pwMS: people with Multiple Sclerosis; SPMS: secondary progressive Multiple Sclerosis; y: years * As the EXPAND study was based on study size compared to the entire cohort, the data from this post-hoc sub-group analysis must be viewed with caution.

5.5. Commentary

5.5.1. Considerations of Patient Selection

Unlike the other S1PRM, siponimod is approved for secondary-progressive MS (SPMS), a phenotype where few therapeutic alternatives exist. In both the product information [3] and the SL [11], the indication of a therapy with siponimod was defined as SPMS with inflammatory disease activity demonstrated by clinical findings or imaging. In the EMA area the approval text references Section 5.1, which refers to the pivotal study [58] that included patients with SPMS without specified disease activity. In our opinion, therapy with siponimod can be considered in individual cases with appropriate prognostic factors (e.g., younger patients with rapid and recent progression), according to recent ECTRIMS/EAN recommendations [12]. However, this is formally an off-label indication with corresponding medico-legal and cost-coverage aspects. We propose a close interaction with a specialized centre.

5.5.2. Considerations of Selected Safety Aspects

Siponimod is a selective S1PRM of S1PR1 and S1PR5. In addition to receptor selectivity [60], other pharmacological aspects such as partial agonism/antagonism, precise targeting of the S1P receptor, and pharmacokinetics presumably contribute to the differences between the various S1PRMs [61,62].

For siponimod, special attention should be paid to genotyping for the hepatic cytochrome P450 metabolism system CYP2C9 prior to the initiation of this therapy. This is because patients who are homozygous for CYP2C9*3 (0.3–0.4% of the population) should not be treated with siponimod due to their insufficient metabolism and hence accumulation of this drug. Patients with CYP2CP*2*3 (1.4–1.7% of the population) or CYP2C9*1*3 (9–12% of the population) should take a reduced maintenance dose of 1 mg per day, whereas a dose of 2 mg per day should be chosen for other genotypes. An informed consent form must be signed for this genotyping. In addition, for this analysis to be covered it must be indicated by physicians with a Swiss post-graduate qualification in clinical pharmacology and toxicology.

In patients taking siponimod in the EXPAND study [58] the most frequent neoplasm was basal cell carcinoma, but there was no statistically significant difference compared to the placebo group. Other skin tumours were also reported in patients taking siponimod. A dermatological evaluation prior to therapy initiation and under treatment is prudent given the context of the advanced age of this patient population. In addition, it should be taken into account that Switzerland ranks high in a European and worldwide comparison of melanoma and basal cell carcinoma rates [63,64], which primarily affect older patients. There are no data available on the possible rebound activity caused by the discontinuation of siponimod. There might be an increased risk of seizures in siponimod-treated patients (2% in siponimod arm vs. <1% in placebo arm in a phase III trial [58]). A similar signal of increased seizures was not seen for fingolimod in a paediatric MS trial (5.6% in fingolimod arm vs. 0.9% in IFN arm [65]), which might indicate a class effect. One case of PML has been reported in September 2022 by the manufacturer [66].

5.6. Considerations of Selected Safety Aspects for Newly Approved S1PRM

In the Table 7. below, we highlight selected safety aspects and differences between the newly approved S1PRM.

Table 7. Safety aspects and differences between the newly approved S1PRM.

Substance	Ozanimod [52,53]	Ponesimod [57]	Siponimod [58]
Mean and maximum decrease of ALC [3,67]	About 60% and up to 68%	About 60% and up to 70%	About 65% and up to 70%
Time to recovery of ALC [67]	1–3 months	7 days	7–10 days
VZV vaccination	In all VZV-seronegative patients	In all VZV-seronegative patients	In all VZV-seronegative patients
Macular oedema screening	In patients with risk factors *	In all patients	In patients with risk factors *
ECG monitoring **	In patients with certain heart conditions [3]	In patients with certain heart conditions [3]	In patients with certain heart conditions [3]
Dose titration	7 days	14 days	6 days
Dermatological controls ***	Prior to therapy initiation and periodically under treatment	Prior to therapy initiation and periodically under treatment	Prior to therapy initiation and periodically under treatment
FEV1 measurement	In case of respiratory symptoms	In case of respiratory symptoms	In case of respiratory symptoms

* Diabetes mellitus, uveitis or retinal disease ** all patients need an ECG prior therapy initiation *** see also section considerations on selected safety aspects of siponimod Abbreviations: ALC: absolute lymphocyte count; ECG: electrocardiogram; FEV1: forced expiratory volume in 1 s; VZV: varicella zoster virus; S1PRM: sphingosine 1 phosphate receptor modulator.

6. Drugs Already Authorised Prior to 2019

Here, we briefly address the novel aspects of drugs approved before 2019 that were not covered in our previous commentary.

Alemtuzumab (Lemtrada®) indication information Table 8.

Table 8. Alemtuzumab (Lemtrada®).

Indication According to Swiss Product Information [3]	*Indication According to the SL* [11]	*Indication According to EMA Product Information* [41]
Lemtrada® is indicated for disease-modifying monotherapy in adult patients with highly active, relapsing–remitting multiple sclerosis (RRMS) despite previous treatment with a complete and adequate cycle of at least one disease-modifying therapy. The benefit/risk assessment of the use of Lemtrada® must be assessed for each patient prior to initiating treatment and then regularly during treatment. Therapy with Lemtrada® may only be initiated by an experienced neurologist in a hospital with direct access to intensive care treatment. The facility in question must have appropriate specialists, medicines and equipment available to identify and treat any adverse reactions that occur, some of which are described below. Especially on initiating treatment, but also during further cycles, Lemtrada® can cause the following serious and potentially fatal adverse reactions: cytokine release syndrome, (anaphylactic) reactions during infusion, myocardial ischaemia and myocardial infarction, haemorrhagic strokes, cervicocephalic artery dissection, pulmonary alveolar bleeding, thrombocytopenias, auto-immune diseases and infections.'	'Valid until 31.12.2024: For adult patients with highly active, relapsing–remitting multiple sclerosis (RRMS) who have previously received a complete and adequate treatment with at least two other disease-modifying therapies (DMTs), or in patients with highly active RRMS for whom all other DMTs are contraindicated or are otherwise not suitable. Due to its safety profile, LEMTRADA® may only be administered by experienced FMH neurologists as a reserve treatment in neurological training category A and B clinics (with access to intensive care treatment). LEMTRADA® can only be reimbursed for a maximum of 4 cycles. The treatment requires confirmation of cost coverage by the health insurer after prior consultation with the attending doctor.'	'The following "measures to minimise the risk of the severe adverse reactions to the drug Lemtrada® for treating multiple sclerosis" were adopted by the EMA on 16.01.2020: On 14 November 2019, the EMA recommended restricting the use of the drug Lemtrada® (alemtuzumab) to treat multiple sclerosis due to reports of rare but serious adverse reactions, including death. In addition, new measures were recommended to identify and manage the serious adverse reactions. The adverse reactions include heart and circulatory diseases (affecting the heart, circulation and haemorrhaging, along with strokes) and immunological disorders (caused by the body's immune system not functioning properly). Lemtrada® should now only be used to treat relapsing–remitting multiple sclerosis if the disease is highly active despite treatment with at least one disease-modifying therapy or if the disease rapidly worsens. Lemtrada® must also no longer be used in patients with specific heart, circulation or bleeding disorders or in patients with other auto-immune diseases other than multiple sclerosis. The drug should only be administered in a hospital with easy access to intensive care facilities and specialists who can treat serious adverse reactions. Furthermore, the EMA recommended updating its doctors' guidelines and patient information leaflets with advice on how to minimise the risk of severe cardiovascular disorders that can suddenly occur after infusion with Lemtrada® (drip infusion) and immunological disorders that can occur many months and possibly years after the last treatment.'

6.1. Commentary

The more restrictive indication of the drug compared to the pivotal studies [68,69] follows the occurrence of relatively rare, but potentially serious, adverse drug reactions in post-marketing pharmacovigilance [70]. These include an increased risk of (haemorrhagic) strokes, cervical artery dissections, and myocardial infarctions in temporal association with the last infusion (<30 days). A safety review of the drug was conducted by the EMA in 2019 using the manufacturer's safety database between September 2013 and April 2019 (corresponding to a total exposure of around 55,000 patient-years) [41,66].

New Aspects since 2019

The indication according to the Swiss product information [3] has been adjusted so that the failure of only one previous therapy is now required (2019; two previous medications). While the extent of the disease activity in treatment naïve patients was defined in 2019 (at least two relapses in the two previous years and at least one relapse in the previous year), there is currently no further definition of "highly active RRMS". In contrast, the SL [11] stipulates that alemtuzumab may only be used in highly active RRMS if at least two previous therapies have been administered or other therapies are contraindicated or unsuitable. It is essential to note that no generally accepted definition of the term "highly active" exists, and assessment depends on the patient's individual situation. This is therefore a judgement call, which is subject to the appropriate assessment of the individual case and is in the competence of the treating physician [1]. In the authors' view, alemtuzumab should be used as a reserve medication after careful evaluation, ideally in collaboration with a specialized centre.

The indication and conduction of therapy with alemtuzumab should take place in a neurological centre with a multi-disciplinary team to treat potentially life-threatening complications and with sufficient expertise in the treatment of MS. This is reflected by the current limitation of alemtuzumab therapy to neurological training category A and B clinics in Switzerland with access to intensive care [11]. Again, this argues for a close interaction between neurologists of different levels of patient care.

Cladribine (Mavenclad®) indication information Table 9.

Table 9. Cladribine (Mavenclad®).

Indication According to Swiss Product Information [3]	*Indication According to the SL* * [11]	*Indication According to EMA Product Information* [41]
'Mavenclad® is used to treat adult patients with highly active, relapsing–remitting multiple sclerosis (MS) defined by clinical or imaging findings.'	Temporary limitation until 30 May 2022.'As disease-modifying monotherapy for highly active, relapsing–remitting forms of multiple sclerosis (MS) in the following patient populations: - Patients with high disease activity despite treatment with a disease-modifying therapy (usually for at least 6 months), or - Patients with rapidly progressive relapsing–remitting multiple sclerosis, defined by 2 or more disabling relapses in a year and with 1 or more gadolinium-enhancing lesions on a brain MRI or with a significant increase in T2 lesions compared with a recent MRI. The treatment requires confirmation of cost coverage by the health insurance after prior consultation with the medical examiner.Treatment by a Swiss Medical Association (FMH) neurologist with timely access to MRI.'	'MAVENCLAD ® is used to treat adult patients with highly active, relapsing–remitting multiple sclerosis (MS) defined by clinical or imaging findings.'

* An update of the limitation is expected by 1 January 2023.

6.2. Commentary

In contrast to the above-mentioned indications for 'highly active' relapsing (remitting) multiple sclerosis, according to the product information [3] and SL [11], the pivotal study on cladribine required one relapse in the year prior to baseline, with no requirements for relapse severity or MR parameters [71]. As with other drugs, disease activity is ill-defined in the approval of cladribine in Switzerland; however, it is specified in the SL with the need for confirmation of cost coverage after consultation with the medical examiner of the health insurance. Since there is no generally applicable definition of the term 'highly active', this is therefore a judgement call subject to appropriate assessment by the treating physician on a case-by-case basis. The confirmation of cost coverage should not lead to a time delay with a potentially urgent treatment for a vulnerable patient group [1,2].

In February 2022, the EMA issued a warning on hepatotoxicity. Prior to starting treatment with cladribine special attention needs to be put on potential hepatic diseases and former drug-induced liver injury, and regular monitoring of liver enzymes is advised. If a patient develops liver failure during treatment with cladribine, the treatment should be paused or discontinued [41]. In this context, Hy's law can be helpful, which consists of the following conditions: (1) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation of >3× the upper limit of normal (ULN); (2) total bilirubin (TBL) increase of >2× ULN; (3) absence of initial findings of cholestasis (absence of an increase in alkaline phosphatase [ALP] to >2× ULN); and (4) no other reason can be found to explain the combination of increased ALT and TBL, such as viral hepatitis, other pre-existing or acute liver disease, or another drug capable of causing the observed injury [72]. We recommend assessing liver function tests (ALT, AST and TBL) prior to the initiation of treatment in year 1 and 2 and a low threshold for the involvement of a hepatologist in the case of suspected hepatotoxicity.

Dimethyl fumarate (Tecfidera®) indication information Table 10.

Table 10. Dimethyl fumarate (Tecfidera®).

Indication According to Swiss Product Information [3]	*Indication According to the SL* [11]	*Indication According to EMA Product Information* [41]
Tecfidera® is indicated for the treatment of patients aged 13 years and older with relapsing–remitting multiple sclerosis (MS) to reduce the frequency of relapses.'	No restriction.	'Tecfidera® is indicated for the treatment of adult patients with relapsing–remitting multiple sclerosis.'

6.3. Commentary

In November 2020, EMA reported [41] on cases of PML in pwMS with mild lymphopenia (lymphocyte count below the lower normal range but $\geq 0.8 \times 10^9$/l). As a potential mechanism dimethyl fumarate (DMF)-induced overexpression of the inhibitory receptor programmed cell death (PD-1) with impaired T-cell response to John Cunningham polyoma virus (JCPyV) is discussed [73,74]. The risk of PML in DMF-treated pwMS as of August 2020 is estimated to be 0.02 per 1000 patients with an incidence rate of 1.02 per 100,000 patient-years. Prolonged lymphopenia (<0.5 G/L over >6 months) and advanced age (calculated from >54 years) were highlighted as risk factors [74]. According to the manufacturer [75], 11 confirmed PML cases in dimethyl fumarate-treated people occurred worldwide as of 1 September 2021, the majority in pwMS with prolonged and severe lymphopenia, and two of those pwMS died (both had a prolonged lymphopenia). In August 2020, an update of the Swiss product information referred to severe cases of herpes zoster, including disseminated herpes zoster, zoster ophthalmicus, zoster meningoencephalitis, and meningomyelitis, as rare adverse events [3]. Whereas safety reports have not led to a change in the indication, we suggest a high clinical vigilance for PML, especially in elderly pwMS with a lymphopenia, and consultation with a specialized centre. In June 2022, Swissmedic has extended the indication of Tecfidera ® to the treatment of paediatric pwMS

aged 13 years and older based on the phase III CONNECT study, which was presented as a poster at ECTRIMS 2021, but has not yet been published. However, a recent phase II study [76] showed the long-term safety and efficacy of dimethyl fumarate in paediatric pwMS consistent with adult pwMS.

Fingolimod (Gilenya®) indication information Table 11.

Table 11. Fingolimod (Gilenya®).

INDICATION according to Swiss Product Information [3]	*Indication According to the SL* [11]	*Indication According to EMA Product Information* [41]
'Gilenya® is indicated for the treatment of adults, adolescents and children aged 10 years and older with relapsing–remitting forms of multiple sclerosis (MS) to reduce the frequency of relapses and delay the progression of disability.'	'Treatment of relapsing–remitting multiple sclerosis (MS). Initial prescription by the Swiss Medical Association (FMH) consultant for neurology.'	'Gilenya® is used as a disease-modifying monotherapy for highly active, relapsing–remitting forms of multiple sclerosis in the following groups of adult patients, adolescents and children aged 10 years old: - Patients with highly active disease despite a complete and appropriate cycle with at least one disease-modifying therapy or - Patients with rapidly progressive relapsing–remitting forms of multiple sclerosis, defined by two or more relapses with disability progression in one year and with one or more gadolinium-enhancing lesions on a brain MRI or with a significant increase in T2 lesions compared to a recently performed MRI.'

6.4. Commentary

In November 2020, the EMA issued recommendations on minimising the risks of drug-induced liver injury (DILI) [41] after cases of acute liver failure occurred following treatment with fingolimod (FTY). Real-world observational studies have shown anomalies in liver parameters of 2% to 25% pwMS, particularly in older male pwMS, frequently present with elevated transaminases, possibly due to the gender-dependent expression of cytochrome P450 [50]. We recommend assessing liver function tests (including bilirubin) prior to the initiation of therapy and after 1, 3, 6, 9 and 12 months of therapy (periodically thereafter) and up to 2 months after the end of therapy with FTY.

With >327,600 pwMS treated and >1,038,100 patient-years as of August 2022, there have been 61 confirmed and unconfounded PML cases in pwMS treated with FTY; the overall risk for PML on fingolimod therapy is estimated to be around 1.86/10,000 pwMS. Since the marketing approval of 2011, three confirmed PML cases have been reported in Switzerland. The estimated incidence rate of fingolimod-associated PML is 5.88/100,000 patient-years (95% confidence interval 4.49–7.55/100,000 patient-years) [66]. PML risk under FTY could depend on treatment duration and age at initiation of therapy [55,77,78]. Some centres in Switzerland perform a lumbar puncture to exclude the presence of JCPyV DNA prior to switching from the fingolimod to other highly effective therapies, although there is no consensus regarding this procedure in Switzerland as a whole [1,2].

The possibility of the disease severely worsening after discontinuation ("rebound activity") of fingolimod should be considered, particularly with a disease onset at a younger age, in initially highly active disease, previous treatment with natalizumab, and occurrence of lymphopenia < 0.3 G/L in the first 3 months of treatment [79–81]. The exact mechanism of this "rebound activity" is unclear to date; therefore, it is currently unclear whether this is a class effect of all S1PRMs.

Natalizumab (Tysabri®) indication information Table 12.

Table 12. Natalizumab (Tysabri®) intravenous and subcutaneous.

Indication According to Swiss Product Information [3]	*Indication According to the SL* [11]	*Indication According to EMA Product Information* [41]
'The risk of PML (progressive multifocal leukoencephalopathy) must be taken into account when determining the indication and prior to initiating treatment (see "Warnings and Precautions").Tysabri® is indicated for disease-modifying monotherapy of highly active relapsing–remitting forms of multiple sclerosis (MS) in the following patient populations: • Patients with high disease activity despite treatment with a complete and appropriate cycle of at least one disease-modifying therapy (see "Warnings and Precautions" and "Pharmacodynamics" for exceptions and information on wash-out periods). or • Patients with rapidly evolving remitting forms of multiple sclerosis, defined by two or more disabling relapses in a year and with one or more gadolinium-enhancing lesions on a brain MRI scan or with a significant increase in T2 lesions compared with a recent MRI.' 'Tysabri® is indicated for disease-modifying therapy of patients with active, relapsing–remitting forms of MS with a negative anti-JCV antibody status.'	'The risk of PML (progressive multifocal leukoencephalopathy) must be taken into account when determining the indication and prior to initiating treatment. As disease-modifying monotherapy for highly active, relapsing–remitting forms of multiple sclerosis (MS) in the following patient populations: - Patients with high disease activity despite treatment with a disease-modifying therapy (usually for at least 6 months), or - Patients with rapidly progressive relapsing–remitting multiple sclerosis, defined by 2 or more disabling relapses in a year and with 1 or more gadolinium-enhancing lesions on a brain MRI or with a significant increase in T2 lesions compared with a recent MRI.The treatment requires confirmation of cost coverage by the health insurer after prior consultation with the attending doctor. Treatment by a Swiss Medical Association (FMH) neurologist with timely access to MRI.'	'Tysabri® is used in adults for disease-modifying monotherapy of highly active relapsing–remitting forms of multiple sclerosis (RRMS) in the following patient populations: • Patients with high disease activity despite treatment with a complete and appropriate cycle of at least one disease-modifying therapy (DMT) (for exceptions and information on wash-out periods, see Section 4.4 and 5.1). or • Patients with rapidly evolving RRMS, defined by 2 or more disabling relapses in a year and with 1 or more gadolinium-enhancing lesions on a brain magnetic resonance image (MRI) or with a significant increase in T2 lesions compared with a recent MRI.'

6.5. Commentary

The approval text reflects the benefit–risk assessment, particularly concerning the PML risk. According to the manufacturer [82], the global incidence of PML in natalizumab-treated pwMS with standard interval dosing (SID), as of February of 2021, was 3.86/1000 pwMS (95% confidence interval 3.61–4.13) and there have been 853 confirmed PML cases worldwide (of which 850 occurred in pwMS).

In comparison to other drugs, the term 'highly active' is more precisely described in respective approvals of natalizumab. However, the Swiss product information [3] no longer requires JCPyV-negative patients to have a 'highly active' but rather an 'active' form, though without a change in the indication in the SL [11]. In this context, the yearly rate of seroconversion of JCPyV-negative pwMS of 7.3–10.3% has to be considered [83,84]. In highly active JCPyV-negative pwMS, antibody testing should be performed every three months (no consensus between different centres in Switzerland). In our opinion, a greater freedom of therapy indication in Switzerland also requires a high clinical vigilance in JCPyV negative pwMS, as well as a close interaction between neurologists of different levels of patient care.

Moreover, the indication and conduction of therapy with natalizumab should be performed in collaboration with a specialized centre. As outlined in the 2019 version of this commentary, a standardised risk stratification should be carried out to reduce the risk of

carry-over PML when switching from natalizumab and S1P receptor modulator therapies, especially depleting therapies [1,2].

In the Swiss product information (and also for the EMA), the authorised dose is either 300 mg intravenously or subcutaneously every 4 weeks. Importantly, the subcutaneous therapy must be supervised by a doctor and must not be performed at home (at least for the first six injections). The efficacy, pharmacokinetics and pharmacodynamics as well as the safety of subcutaneous natalizumab administration is comparable to intravenous therapy every 4 weeks [85,86]. As a potential approach to reduce PML risk, extended interval dosing (EID) is discussed [87–90]. In a retrospective study, the cumulative probability of PML during long-term treatment was 1.7–2.04/1000 pwMS in the EID group (compared to 4.46–4.74/1000 pwMS in the standard interval dosing (SID) group) [87]. In a phase IIIb study, EID showed comparable efficacy to that of SID, but in the EID group there were two pwMS with extreme new/enlarging T2 hyperintense lesion numbers ($\geq$25) and a pwMS with an asymptomatic PML [91]. The "Warnings and Precautions" section of the Swiss product information [3] was adapted. Compared to the authorised dosing interval, a longer TYSABRI dosing interval (on average about 6 weeks) is suggested for anti-JCV-positive-antibody patients may be related to a lower risk of PML. When applying an EID, caution is advised, as the efficacy of the EID is not proven and the associated risk-benefit-ratio is currently not known. EID is an off-label therapy in Switzerland.

Ocrelizumab (Ocrevus®) indication information Table 13.

Table 13. Ocrelizumab (Ocrevus®).

Indication According to Swiss Product Information [3]	*Indication According to the SL* [11]	*Indication According to EMA Product Information* [41]
'Ocrevus® is indicated for the treatment of adult patients with active relapsing–remitting forms of multiple sclerosis (MS). Ocrevus is indicated for the treatment of adult patients with primary-progressive multiple sclerosis (PPMS) to slow down the progression of the disease and reduce the deterioration in walking speed.'	Temporary limitation until 31.03.2022.'For the treatment of adult patients with active relapsing forms of multiple sclerosis (MS).''For the treatment of adult patients with primary-progressive multiple sclerosis (PPMS) to slow down the progression of the disease and reduce the deterioration in walking speed.'	'Ocrevus® is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis with active disease defined by clinical findings or imaging. Ocrevus is indicated for the treatment of adult patients with previous primary-progressive multiple sclerosis (PPMS), characterised using the disease duration and degree of disability as well as with imaging features that are typical for inflammatory activity.'

6.6. Commentary

In the opinion of the authors, the use of the medication is justified as a first-line and second-line therapy, taking into account individual prognostic risk factors and safety requirements.

The indications in Switzerland have remained unchanged since 2019, according to the product information [3] and SL [11].

As of 01/2022, 10 PML cases have been reported with ocrelizumab, 9 of which were carry-over PML [92]. In 2021, another case report of a 78-year-old PPMS patient undergoing ocrelizumab therapy who died of PML without any previous therapy was published [93]. In this case, grade 2 lymphopenia, B-cell depletion and only mild T-cell reduction were present at the time of PML diagnosis. This case highlights the need for critical indication, especially in elderly, "immunosenescent" pwMS, ideally in collaboration with specialized centres [1,2].

Teriflunomide (Aubagio®) indication information Table 14.

Table 14. Teriflunomide (Aubagio®).

Indication According to Swiss Product Information [3]	*Indication According to the SL* [11]	*Indication According to EMA Product Information* [41]	*Inclusion Criteria and Main Findings of Phase III Study in Pediatric pwMS* [94]
'Aubagio® is indicated for the treatment of adults, adolescents and children aged 10 years and older with relapsing–remitting forms of multiple sclerosis (MS).'	No restriction.	'AUBAGIO® is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS) (please refer to Section 5.1 for important information on the population for which efficacy has been established).'	• age 10–17 years • RRMS • EDSS score ≤5.5 • Active comparator: teriflunomide (randomized in 2:1 fashion) • at least one relapse in the prior year (or at least two relapses in the last two years) • premature change from the double-blind study to the OLE study possible if either clinically confirmed relapse or high activity on MRI (defined as ≥5 new/enlarging T2-lesion at week 24, followed by ≥9 new/enlarging T2-lesions at week 36, ≥new/enlarging T2-lesions at week 36 and 48, or week 48 and 72) • Baseline characteristics: 166 pwMS (mean age 14.6–14.7 y, mean EDSS 1.2–1.4, 75–83% therapy naïve, 2/3 female, mean number of relapses 1.4–1.6 in last 12 months, mean disease duration 1.4 y) • Primary endpoint: probability of confirmed clinical relapse during the double-blind period (up to 96 weeks): teriflunomide 0.39 vs. placebo 0.53, $p = 0.29$ • Adjusted number of new or enlarged T2 lesions per MRI: teriflunomide 4.7 vs. placebo 10.5, $p = 0.00061$ • Adjusted number of T1 gd-enhancing lesions per MRI: teriflunomide 1.9 vs. placebo 7.5, $p < 0.0001$ • Percentage change in brain volume from baseline at 48/96 weeks: teriflunomide −0.11/−0.53 vs. placebo −0.20/−0.57, $p = 0.59/0.87$

Abbreviations: EDSS: expanded disability status scale; gd: gadolinium; MRI: magnetic resonance imaging; OLE: open label extension; pwMS: people with Multiple Sclerosis; RRMS: relapsing remitting Multiple Sclerosis; y: years.

6.7. Commentary

Teriflunomide has recently been authorized (in Switzerland since end of 2021; in the EMA-zone since 07/2021) for the treatment of paediatric pwMS aged 10 years and older [94]. After 96 weeks, no statistically significant difference regarding the primary endpoint of confirmed clinical relapses was seen, whereas there was a reduction in new/enlarging and enhancing lesions on MRI. One potential explanation that the primary endpoint was not met is a premature switch into the open-label extension (OLE) study due to a high activity in MRI, observed more commonly than anticipated in the placebo group (26%, vs. 13% in the teriflunomide group), which may have reduced the power of this study. Adverse effects were commonly seen in both groups (teriflunomide group 88%, placebo group 82%), and severe side effects were seen in both groups (11%). Nasopharyngitis, infections of the upper airways, alopecia, paraesthesia, abdominal pain, and elevated serum creatine–phosphokinase were seen more commonly in the teriflunomide group, and during the double-blind phase, four pwMS treated with teriflunomide developed pancreatic adverse effects, leading to the discontinuation of therapy in three pwMS.

Currently, the TERIKIDS phase III trial is followed by the OLE study over 96 weeks.

7. Commentary on Generic Disease-Modifying Therapies and on off Label Treatment with Rituximab

In 2021, generic disease-modifying therapies for the treatment of MS have been introduced in Switzerland. Bioequivalence with drug levels of a generic product between 80 and 125% of the original drug [44] are required. However, bioequivalence does not necessarily result in the same clinical profile. The authors currently do not recommend switching pwMS to a bioequivalent generic product if patients are stable and do not experience side effects under the original substance. However, an a priori treatment with the bioequivalent product can be considered.

Rituximab is not approved for the treatment of MS; however, it is often used as an off-label therapy following several smaller phase II and phase II/III trials [95,96]. This contrasts to new and approved anti-CD20 monoclonal antibodies with large pivotal phase III trials. In the authors' opinion, off-label therapy with rituximab should only be continued in pwMS with a stable disease course under an adequate safety standard, if patients have been on this therapy for a longer period of time, and if there are no relevant adverse reactions and no safety concerns. In this case, switching to one of the new drugs should not be forced. However, approved drugs should generally be used. In addition, therapy with rituximab in pwMS should be administered in collaboration with a specialized centre and requires individual cost coverage.

8. Commentary on Pregnancy and Breastfeeding in pwMS

A large number of disease-modifying immunotherapies are available for the treatment of MS; however, many of them are contraindicated during pregnancy as well as breastfeeding and some substances have restrictions for male pwMS. Hence, family planning should always be considered in the choice of immunotherapy. If clinically necessary, the continuation of immunotherapy during pregnancy can be considered in exceptional cases for particular substances. In these situations, careful consideration of the benefit–risk profile and interdisciplinary cooperation between the treating neurologist and gynaecologist/neonatologist in a dedicated centre is necessary. As this is a broad topic that warrants special attention, an update regarding immunotherapies in MS with a focus on family planning, pregnancy and lactation is currently in preparation (Graber, Chan) and is set to provide consensus recommendations that are reviewed and agreed upon by the Medico-Scientific Advisory Board of the SMSS and the SNS.

9. Conclusions

With the ever-widening armamentarium of different treatment options, disease-modifying therapy for multiple sclerosis is becoming more successful but also more challenging in its differential indication and monitoring. Table 15 gives an overview of the MS therapy landscape in Switzerland in 2022. Regulatory, administrative, and system-immanent factors lead to Swiss-specific aspects in clinical care. The authors will continue to regularly comment on national developments. However, we also encourage an in-depth discussion regarding the optimal structure of care that meets all the requirements of increasingly specialised forms of therapy and ideally involves neurologists from all levels of patient care.

Table 15. MS therapy landscape in Switzerland in 2022.

		RRMS	RMS	SPMS	PPMS
Highly active * forms	*First-line therapy*	Cladribin Natalizumab			
	Second-line [3]/*third-line* [11] *therapy*	Alemtuzumab			
Active * forms	*First-line therapy*	Natalizumab **	Interferon beta 1b	Interferon beta 1b ****	
		Ocrelizumab Ofatumumab Ponesimod Rituximab ***	Ocrelizumab Ofatumumab	Ocrelizumab Rituximab *** Siponimod	
Labelling without activity specification	*First-line therapy*	Beta-Interferons			Ocrelizumab
		Dimethyl fumarate Diroximel fumarate Fingolimod Glatiramer acetate Ozanimod			

Table 2: **MS therapy landscape in Switzerland in 2022** (Alphabetical order, according to marketing approval text [3,11], see details above).
* No general definition of the terms «active» and «highly active» exists, see details above,
** Only for JCPyV-negative patients. *** Off-label. **** long-term data do not support use of interferons in active SPMS [97]

Abbreviations: JCPyV: John Cunningham Polyoma virus; PPMS: Primary Progressive Multiple Sclerosis; RMS: Relapsing Multiple Sclerosis; RRMS: Relapsing Remitting Multiple Sclerosis; SPMS: Secondary Progressive Multiple Sclerosis. * No general definition of the terms «active» and «highly active» exists, see details above, ** Only for JCPyV-negative patients. *** Off-label. **** long-term data do not support use of interferons in active SPMS [97].

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