Appendix 1

Table 1 - Poor prognosis predictors in MS. Based on ref.[11].

Demographic and environmental factors	Comorbid conditions (e.g. cardiac or cerebrovascular diseases, previous/current malignancy)
	Ethnicity (not of European descendent)
	Low vitamin D levels
	Male sex
	Older age
	Smoking
Clinical factors	Brainstem, cerebellar or spinal cord onset
	Early cognitive deficits
	High EDSS score at diagnosis
	High relapse rate
	Polysymptomatic onset
	Poor recovery from the first relapse
	Primary progressive disease subtype
	Short interval between the first and second relapses
MRI observations	Grey matter atrophy
	High number of T2 lesions
	High T2 lesion volume
	Presence of gadolinium-enhancing lesions
	Presence of infratentorial lesions
	Presence of spinal cord lesions
	Whole brain atrophy
Biomarkers	High levels of chitinase in the CSF
	High levels of NfL in the CSF and serum
	High levels of kappa FLC in the CSF
	Presence of IgG and IgM oligoclonal bands in the CSF
	Retinal nerve fiber layer thinning detected with optical coherence tomography

CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Scale; FLC, free light chain; Ig, immunoglobulin; MRI, magnetic resonance imaging; NfL, neurofilament light chain.

Table 2. Overview of the disease-modifying therapies for MS approved by EMA. The information is based on the Summary of Product Characteristics (SmPC) for each medication.

Active Principle	EMA approved indication (SmPC)	Pharmacotherapeutic Classification	Mechanism of Action
Injectables			
IFNβ-1b (SC)	CIS, RRMS, aSPMS	Immunostimulant	(Not defined)
IFNβ-1a (IM)	CIS, RRMS, aSPMS		
IFNβ-1a (SC)	RMS (RRMS and aSPMS)		
Pegylated-IFNβ-1a (SC)	RRMS		
Glatiramer acetate (SC)	RMS (RRMS and aSPMS)		
Ofatumumab (SC)	RMS (RRMS and aSPMS)	Anti-CD20 monoclonal antibody	Depletion of B cells
Intravenous			
Mitoxantrone[a]	HA-RMS (RRMS and aSPMS)	Anthracenedione-derived antineoplastic agent	Depletion of B and T cells, inhibition of macrophage proliferation
Natalizumab (IV, SC)	HA-RRMS and RES-RRMS	Alpha-4-integrin inhibitor	Inhibition of immune cell migration (through the BBB) into the CNS
Alemtuzumab	HA-RRMS and RES-RRMS	Anti-CD52 Monoclonal antibody	Depletion of lymphocytes
Ocrelizumab (IV, SC)	RMS (RRMS and aSPMS), aPPMS	Anti-CD20 monoclonal antibody	Depletion of B cells
Ublituximab[b]	RMS (RRMS and aSPMS)		
Oral			
Teriflunomide	RRMS	Dihydroorotate dehydrogenase inhibitor	Inhibition of activated lymphocytes proliferation
Dimethyl fumarate	RRMS	Immunosuppressant	(Not defined)
Cladribine	HA-RMS (RRMS and aSPMS)	Synthetic purine nucleoside analog	Depletion of B and T cells
Fingolimod	HA-RRMS and RES-RRMS	S1P receptor modulator	Migration inhibition of immune cells/lymphocytes from lymph nodes into the bloodstream and CNS
Siponimod	aSPMS		
Ozanimod	RRMS		
Ponesimod[b]	RMS (RRMS and aSPMS)		

a: declining application due to severe side effects. b: not yet approved for MS treatment in Portugal.

BBB, blood-brain barrier; CIS, clinically isolated syndrome; CNS, central nervous system; EMA, European Medicines Agency; HA, highly active; IFNβ, interferon beta; IM, intramuscular; IV, intravenous; MRI, magnetic resonance imaging; MS, multiple sclerosis; PPMS, primary progressive MS; RES, rapidly evolving severe; RMS, relapsing forms of multiple sclerosis; RRMS, relapsing-remitting MS; S1P, sphingosine-1-phosphate; SC, subcutaneous; SPMS, secondary progressive MS.