Overview of the patent status of MS treatments

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Introduction

The information below is provided for educational purposes only and does not constitute legal advice. This report provides a snapshot at a point in time and may not be comprehensive.
Various types of patents may be granted for pharmaceuticals. In general, a patent covering the specific active molecule (a 'product patent') is considered 'strongest', that is, most likely to prevent generic products from entering the market. Other types of patents, sometimes termed 'secondary' patents, can cover aspects such as method of use, specific formulations (e.g. formulation as a tablet with specific excipients) or production methods.
Information concerning the main patents and patent applications for the selected products was collected from sources such as the FDA Orange Book or Canada Health patent register, regional or national patent office databases, and the originator's submissions to patent offices.
While in general it is safe to assume that an unexpired product patent, where it is granted and in force, will block generic entry, whether secondary patents block generic market entry is a more difficult question. In many cases, generic manufacturers can 'invent around' secondary patents to avoid infringement.
The patent searches were limited to a few sample countries, including countries where several leading generic manufacturers are located (e.g. Brazil, China, India, South Africa, Thailand), relevant regional patent offices (ARIPO, EAPO and OAPI) and an illustrative sample of LMICs from other regions (e.g. Guatemala, Indonesia, Morocco, Ukraine and Vietnam).

Patent Status / Acronyms and abbreviations

G	granted
F	filed/pending
N	not in force (abandoned, expired, withdrawn, invalidated)
.	not filed
u	Status unknown
*	No EAPO filing but national filing in Russia (RU)

Countries/Regional patent organisations

ARIPO	African Regional Intellectual Property Organization (19 states)
BRA	Brazil
CHN	China
EAPO	Eurasian Patent Organization (8 states including Russia)
EPO/EP	European Patent Organization (covers most of European countries. In addition, European patents can for example be validated in Morocco if filed on or after 1 March 2015, in Tunisia if filed on or after 1 December 2017 and Cambodia.
GTM	Guatemala
IDN	Indonesia
IND	India
MAR	Morocco
OAPI	Organisation Africaine de la Propriété Intellectuelle (17 states)
PHL	Philippines
THA	Thailand
UKR	Ukraine
US	Unite States of America
VNM	Vietnam
ZA	South Africa

Contents

A. On-label MS treatments

Patent information provided on 08.03.2022

1. Daclizumab [Zinbryta®; Biogen; US FDA 27.05.2016]

Daclizumab, developed by Roche/Protein Design Labs, was approved as Zenapax® for the prevention of organ rejection after renal transplantation in 1999 (by EMA, withdrawn today) and for the treatment of MS as Zinbryta® in 2016 by EMA and health Canada). Zinbryta® has since been withdrawn in Canada (in 2018) and in EU. Patents on the antibody itself were filed mainly in HICs and expired. Secondary patents on the use in MS granted in HICS and are expected to exprire in 2023.

Description	Patent Publication #	Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
daclizumab US5,530,101, see SEQ LO NO: 5 and SEQ ID NO: 7 for the heavy and light chain variable regions	WO9211018 (Protein Design Labs)	19.12.2011															N	N
Stable liquid pharmaceutical formulation of IGG antibodies (exemplified with daclizumab)	WO03039485 (Protein Design labs, collaboration with Biogen)	08.11.2022							G								G	G
Use of an IL-2R antagonist to treat MS (in the absence of treatment with beta interferon)	WO2004002421 (US GOV HEALTH & HUMAN SERV)	27.06.2023															G	G

2. diroximel fumarate [Vumerity®; Biogen; 29.10.2019 in US for MS)

Vumerity®, approved in the US in 2019 to Biogen, is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. Diroximel fumarate (previously ALKS 8700) was developed by Alkermes who entered into a license and collaboration agreement around this candidate with Biogen in 2017.

Patent applications on the compound were filed and granted in many HICs and LMICS. The expected 20 years expiry date is 14.03.2034.

Description	Patent Publication #	Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
Prodrugs of fumarates and their use in treating various diseases (MS & proriasis)	WO2014152494 (Alkermes)	14.03.2034	.	F	F	G	.	G	G	.	.	.	.	G	G	.	G	G

3. laquinimod (withdrawn)

Teva signed an agreement with Swedish company Active Biotech in June 2004 for the development and commercialisation of laquinimod, a small molecule candidate developed as potential therapy for

neurodegenerative diseases, including multiple sclerosis (MS) and Huntington's disease (HD). In 2014, the marketing authorisation for the use of Nerventra®/laquinimod in MS was refused by the EMA (see EMA Nerventra). In 2018, Teva abandoned the development and returned the rights to laquinimod to Active Biotech who is currently investigating its effects for the treatment of non-infectious non-anterior uveitis.

According to a quick patent search in WIPO Patentscope, Teva filed between 2009 and 38 international patent applications around laquinimod. The primary patent on the compound was filed by Active Biotech in 1999 in numerous LMICs and HICs. The compound patents have expired or were abandoned worldwide.

Description	Patent Publication #	Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
Laquinimod compound and use in MS	WO9955678 (Activ Biotech)	26.04.2019	N	N	N	N*		N	N	.	N	.	.	N	N	N	N	N

4. ofatumumab [Kesimpta®; Novartis; EU 30.03.2021]

Ofatumumab was first developed by Genmab. GSK assumed development responsibility of ofatumumab for autoimmune indications in 2010 (source). Novartis acquired the rights to GSK's Ofatumumab to develop treatments for MS and other autoimmune indications in 2015 (source).

ARZERRA (ofatumumab) Injection, for intravenous infusion – was initially approved by USFDA to GSK in 2009 for the treatment of leukemia. It was approved by EMA in 2010 and has now been withdrawn. KESIMPTA® (ofatumumab) injection, for subcutaneous use for the treatment of relapsing forms of multiple sclerosis was approved by US FDA to Novartis on 20.08.2020 and by Health CA on 08.04.2021 and EMA on 30.03.2021.

Patents on the antibody itself and its use to treat several diseases including MS, granted in India and few other LMIcs, are expected to expire on 17.10.2023. In Russia the patent term is extended until 2027 and in Kazakhstan until 2028. A secondary patent on the formulation was filed in numerous LMCIs and is expected to expire in 2028.

Description	Patent Publication #	Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
Ofatumumab and uses (including MS)	WO2004035607 (GENMAB)	17.10.2023	.	G	G	G # RU 27 KZ 28	.	.	G	.	.	.	.	G	.	.	G	G
Antibody formulations	WO2009009407 (GSK)	03.07.2028	.	G	G	G only RU, KZ	.	G	G	G	.	G	G	G	G	G	F	G

5. ozanimod [Zeposia®; Celgene; Helath CA 12.11.2020]

Ozanimod, an S1P receptor modulator, was acquired by Celgene from Scripps in 2016 and was first approved for the treatment of relapsing forms of multiple sclerosis in the US early 2020 and in Canada in November 2020.

Patents on the compound were filed and granted in a limited number of LMICS (including India) and are expected to expire in 2029.

Description	Patent Publication #	Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
Novel modulators of sphingosine phosphate receptors	WO2009151529 (Scripps Research Int)	14.05.2029	.	F	G	G	.	.	G	.	.	G	.	.	.	.	G	G

6. ponesimod [Ponvory®; Janssen; USFDA 18.03.2021; Health CA 01.11.2021]

Ponesimod, an S1P receptor modulator, indicated for the treatment of relapsing forms of multiple sclerosis (MS) was approved by USFDA early 2021 and in Canada in November 2021. It was developed by Actetion, a company acquired by Janssen in 2017 (source).

Patents on the compound were granted in a limited number of LMICs (including India) and are expected to expire in November 2024. Patents on the crystalline form are expected to expire in 2029 and patents on a specific treatment regimen in 2035.

Description	Patent Publication #	Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
Compound - 5-(BENZ- (Z) -YLIDENE) -THIAZOLIDIN-4-ONE DERIVATIVES AS IMMUNOSUPPRESSANT AGENTS	WO2005054215 (Actelion)	16.11.2024	.	G	G	G*	.	.	G	.	.	G	.	.	G	.	G	G
Crystalline forms of (r) -5- [3-chloro-4- (2, 3-dihydroxy-propoxy) -benz [z] ylidene] -2- ([z] -propylimino) -3-0-tolyl-thiazolidin-4-one	WO2010046835 (Actelion)	19.10.2029	.	F	G	G*	.	.	N	.	.	G	F	.	G	.	G	G
Dosing regimen for a selective s1p1 receptor agonist	WO2016091996 (Actelion)	10.12.2035	.	.	F	G				G		F	G	G				G

7. siponimod [Siponimod fumaric acid (Mayzent®; Novartis; US 26.03.2019)

MAYZENT is a sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (MS). It was approved in the US on 26.03.2019 and in Canada on 24.04.2020. According to the US label MAYZENT tablets contains Siponimod as 2:1 co-crystal of siponimod and fumaric acid.

The expected twenty-year expiry for the compound patents is 19.05.2024. It was filed and granted in few LMICs, including India. Patents on the hemisulfate salt are expected to expire in 2029. A patent om a specific treatment regimen was filed in a limited number of LMICs with an expected expiry in 2029. A patent ion the formulation was filed in a large number of LMICs and has an expected expiry in 2032

Description	Patent Publication #	Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
Siponimod **compound** and compositions	WO2004103306 (IRM LLC; Novartis)	19.05.2024	.	G	N	G*	.	G	G	G	.	G	.	.	G	.	G	G
Siponimod **hemifumarate salt**	WO2010080409 (Novartis)	16.12.2029	.	F	F	G*	N	G	F	G	.	G	F	.	G	.	F	G
Dosage regimen of an S1P receptor agonist (dosage lower than the standard daily dosage of said S1P receptor modulator or agonist during the initial period of treatment and then the dosage is increased, up to the standard daily dosage of said S1P receptor agonist.)	WO2010072703 (Novartis)	21.12.2029		N	F	G*			.	G		G	N		G		G	G
Immunosuppressant **formulations** (admixture with one or more non-basic compounds)	WO2012093161 (Novartis)	05.01.2032	.	F	G	G	F	G	G	G	.	G	F	N	G	.	F	G

Patent information provided on 13.06.2019

8. Alemtuzumab [Lemtrada®; Genzyme; US 2001]

Alemtuzumab is and antibody anti-human CD-52. Its use in MS was approved in the US to Genzyme in 2001 under the brand Lemtrada®. The product Campath® has previously been approved for the use in Leukemia. Patents on the antibody itself expired in 2019. Patent applications on a specific treatment regimen (in the US label) were filed in few LMICs

Description	Patent Publication #	Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
An antibody binding to the antigen Campath-1	WO8907452 (Medical Research Council)	2009															G	G 2014#
CDw52-specific antibody (Alemtuzumab) for treatment of MS	WO9310817	2012														N	N	N
Treatment Regimen in MS with Alemtuzumab (first treatment cycle of at a dose of 12 mg/day for five days and 12 months after said first treatment cycle with a further treatment cycle of Campath-1 H at a dose of 12 mg/day for three days)	WO2008031626 (Genzyme, Bayer)	2027	.	F	G	G*	.	.	N	.	.	.	F	.	G	.	G	G

9. Cladribine [Mavenclad®, EMD Serono/Merck KGaA; US 2019]

Cladribine compound patent expired in 2005. A patent on the oral formulation of cladribine (with cyclodextrin) was granted in India, China, South Africa, EP and US and is pending in Brazil. A patent on cladribine treatment regimen for MS was filed in several countries and granted so far in EP, US, ZA, UA, EA and is pending in CN. In India this application was abandoned.

Description	Patent Publication #	Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
Cladribine product	US4760137	2005																
Oral formulation of cladribine (with cyclodextrin)	WO2004087101 (Merck KGaA)	2024	.	F	G	G	.	.	G	.	.	.	.	.	G	.	G	G
Treatment regimen for MS with cladribine-free periods	WO2006067141 (Serono)	2025	.		F	G	.		N	.	.			G	G	.	G 2026	G

10. Dimethyl fumarate [Tecfidera®; Biogen; US 2013]

Dimethyl fumarate per se is off patent. The product is known since the 60's and patents on its use in psoriasis were filed in 1985. Patents on the use in autoimmune diseases were filed in 1999 and will expire worldwide in October 2019 except for few European countries where supplementary patent protection was obtained until 2024. Secondary patents on specific treatment regimens with an expected expiry date in 2028 were only filed in HICs.

Description	Patent Publication #	Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
Fumaric acid derivatives and their use for the treatment of psoriasis.	EP0188749	2005																
Micropellets of microtablet preparations comprising dialkyl fumarates (e.g. dimethyl fumarate) & their use in autoimmune diseases	WO0030622 (Fumapharm, acquired by Biogen)	29.10.2019	.	C	G	G*	.	.	G	.	.	.	.	.	.	G	G	G 2024#
A method of treating MS with an oral composition of dimethyl fumarate, monomethyl fumarate, or a combination thereof, the effective amount of the compounds or combination being of about 480 mg per day	WO2008097596	2028 - HICs only															G	G

11. Fingolimod [Gilenya®]

The main product patent on **fingolimod** appears not to have been filed in the LMIC jurisdictions surveyed. However, two formulation patent families, expiring in 2024 and 2032, have been widely granted, with the exceptions of ARIPO, OAPI, and Vietnam.

In the US, the first formulation patent US 8,324,283 B2 relating to fingolimod compositions with sugar alcohol (expiry date in 2026), was found invalid by the U.S. Court of Appeals for the Federal Circuit agreeing thereby with a 2015 decision by the U.S. Patent Trial and Appeals Board decision. The US patent on the dosing regimen, US 9,187,405 B2 (expiry date in 2027) was also challenged by several generic companies but was upheld by the U.S. Patent and Trademark Office in a decision issued in July 2018. The generic companies (Apotex, Argentum, Actavis, Teva and Sun) have already appealed the decision and Novartis, has in turn filed lawsuits against them. The patent on the second formulation (cyclodextrin as a stabiliser), US 9,592,208 (expiry date in 2032), covers specifically the composition of 0.25 mg capsule [the reference standard for the FDA being the 0.5 mg capsule].

Regarding the secondary patents on fingolimod (expiring 2024 and 2032), further consultation would be necessary to establish whether these represent a true block to generic market entry. This may depend on whether it is possible to develop non-infringing alternative formulations while achieving bioequivalence.

The first generic of Gilenya, Nescler, has been approved in Russia and Belarus in 2014 and 2016 respectively to the company BioIntegrator LLC.

Description	Patent Publication #	Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
Product patent	WO9408943	2014	.	.	.	.	.	.	.	.	.		.	.	.	.	.	.
Formulation patent - solid composition of fingolimod & sugar alcohol	WO 2004/089341	2024	.	G	G	G* 2025#	.	G	G	G	.		F	.	G	.	G	.
Method of use in multiple sclerosis – RRMS with a daily dose of 0.5 mg of fingolimod	WO 2008/000419	2027	.	G	G	G*	.	.	N	.	.		.	.	.	.	.	.
Formulation patent - solid composition comprising fingolimod and phosphate derivative, filler, cyclodextrin as stabilizer	WO 2012/135561	2032	.	G	G	G	G	G	G	G	.		F	G	G	.	G	.

12. Glatiramer acetate [several brand names but innovator was Copaxone®]

The patents on **glatiramer acetate** filed in 1994 by Yeda Research and Development Co., Ltd have expired in 2015. In the LMIC jurisdictions surveyed, secondary patents expected to expire in 2030 and relating to a specific treatment regimen of RRMS with glatiramer acetate have been granted in EAPO, and Ukraine and are pending in Brazil, China, India (application under opposition). The equivalent patents in the USA have not prevented the entry of generic versions of **glatiramer acetate** which are also available in other countries.

Description	Patent Publication #	Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	EP	US
Product, compositions and manufacturing process	WO95/31990	2014-2015	.	N	N	N	.	N	.	.	.		.	N	N	.	N	N
Treatment regimen of RRMS with glatiramer Acetate	WO 2011/022063	2030	.	F	F	G	.	F/C	.	.	.		.	G	F	.	G	G

13. Interferon-beta 1a [Avonex® and Rebif®]

Interferon-beta was purified and characterised in 1976 (E. Knight, Jr., Proc. Natl. Acad. Sci. USA 73, 520 (1976) and its production by recombinant DNA technology is known since the 80's. It is therefore safe to consider that any basic patents on Interferon-beta and its production by recombinant technology have now expired.

Although basic patents have expired, each of the products below is covered by secondary patents on the formulations, processes of manufacturing or devices (e.g. Pens).

Rebif®, Serono Inc, US 1996 - production by CHO cells

Description	Patent Publication #	Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
IFN-β liquid formulations stabilized with mannitol (**REBIF**)	WO95031213 (Merck Serono)	2015																
IFN HSA-free liquid formulation with cyclodextrin, mannitol and polaxamer (**Rebif new formulation**)	WO2004096263	2024	.		G	G	.		G	.	.			G	G	.	G	G
Process for manufacturing glycosylated recombinant human interferon beta (step in a serum-free medium)	WO2007022799	2025	.	G	G	G	.	.	G	.	.	.	.	.	F	.	G	G
A stabilized HSA-free liquid pharmaceutical comprising a buffer, an amino acid and an antioxidant	WO2005117949	2025	.	F	G	G	.		N	.	.			G	G		G	G

Avonex®; Biogen, US 1996 - production by CHO cells

Description	Patent Publication #	Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
DNA sequences, recombinant DNA molecules and processes for producing human fibroblast interferon-like polypeptides - **listed in health Canada for Avonex**	CA2269201 (Biogen)	2001																

14. Interferon-beta 1b [Betaferon® and Extavia®]

Betaferon®; Bayer (Schering, Berlex), US 1993 - Production in E. Coli

Description	Patent Publication #	Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
Human Interferon-Beta Formulations	WO03006053 (Schering)	2022							.								F	

Description	Patent Publication #	Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
Recombinant Human Interferon-Beta-1bPolypeptides & production processes	WO2005016371 (Schering)	2024	.	F	G	F*	.	F	N	.	.	A	.	F	G	.	F	G

Interferon-beta 1b - Extavia®, Novartis (Chiron), US 2009 - Production in E. Coli

Description	Patent Publication #	Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
IFN-β or variant thereof and highly purified mannitol	WO0238170 (Chiron)	2021																

15. Natalizumab [Tysabri®; Biogen, US 2004]

The patents on antibodies anti human integrin alpha-4 (Natalizumab) expired in 2015 except in few countries in Europe where paediatric extensions of Supplementary Protection Certificates were obtained until January 2020. Patents on the liquid formulation of natalizumab should expire in 2024.

Description	Patent Publication #	Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
humanized antibodies anti human integrin alpha-4 (natalizumab)	WO9519790 (Elan)	2015 EP 2020 Ped exc															G	G 2020#
Natalizumab liquid formulation	WO2004071439	2024	.	.	F	.	.	.	G	.	.	.	F	.	.	G		G

16. Ocrelizumab [Ocrevus®]

Ocrelizumab is protected by a product patent expiring in 2023 in many jurisdictions (Table). It has generally been filed or granted in the countries/regions surveyed except in ARIPO, OAPI, and Guatemala. It is likely that biosimilar ocrelizumab cannot enter the market where this patent has been granted, before 2023. A secondary patent family, expiring 2029, is granted in China and South Africa, and pending in Brazil and Thailand, but has not been filed in other LMIC jurisdictions that were surveyed. Due to a delay in publication, it is not possible yet to comprehensively assess coverage by a secondary patent family expiring 2035/36.

Regarding the secondary patents on ocrelizumab (expiring 2029, possibly as late as 2036) further consultation would be necessary to establish whether these represent a true block to generic market entry. This may depend on the practical enforceability of method-of-use patents in each jurisdiction.

Description	Patent Publication #	Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
Product patent	WO04056312 WO04060052 WO04060053	2023	.	F	G	(G in RU	.	G	G	G	.		F	G	G	G	G 25-28†	G 28-29#

Description	Patent Publication #	Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
						& BY)*												
Method of use in MS - progressive multiple sclerosis	WO 2010/033587	2029	.	F	G	F	.	.	N	.	.		F	.	G	.	G	F
Method of use in MS - Improving functional ability in a patient with MS	WO 2017/062682	2036	.	.	F	F*	.	.	.	.	.	.	.	.	.	.	.	F

17. Peginterferon-beta 1a [Plegredy®, Biogen, EU 2014]

Description	Patent Publication #	Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
Polymer conjugates of interferon beta-1a and their uses	WO0023114 (Biogen)	2019 (OCT)		G	G	G			.								G	G
Activated polyalkylene glycol polymers	WO03061577 (Biogen)	2023	.	F	F	F	.	F	G	.	.	F	.	F	F	.	F	F
Method for storing/delivering IFN-beta in a device (PEN)	WO2006076453 (Biogen)	2026	.	F	F	.	.	.	G	.	.	.	.	.	.	.	G	G

18. Teriflunomide [Aubagio®, Sanofi Aventis; US 2012]

Teriflunomide product patent expired in 2010. Patent applications on its use in MS were filed and granted only in HICs. A patent on a tablet formulation was filed widely with an expiry date in 2030.

Description	Patent Publication #	Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
Compound patent (generic disclosure) & use in cancer and rheumatoid diseases	WO9117748 (Hoechst)	2010																
Use of teriflunomide in MS	WO02080897 (Aventis)	2022	.		.				.								G 2026	G
Teriflunomide tablet formulations without colloidal silicon dioxide	WO2011032929 (Sanofi)	2030	.	F	F	F*	F	F	G	G	.	F	F	G	G	G	G 2030	G
Method for co-administering rosuvastatin with teriflunomide in a patient with MS	US9186346 (Sanofi)	2033	.	.	.	.	.	.	.	.	.	.	.	.	.	.	G	F

B. Off-label treatments

The product/compound patents for all products listed under this section have now expired. Secondary patents on specific formulations may however exist.

Patent information provided on 23.02.2022

19. intravenous immunoglobulin - IVIG (off-label)

No search done.

20. minocycline (off-label)

Minocycline, a second-generation tetracycline antibiotic, was patented in the 60's (US3226436, Merck Index). The compound per se is off patent. Many generics approved in the US with patents on devices or extended-release formulation.

21. mycophenolate mofetil (off-label)

Mycophenolate mofetil was approved to Roche in 1995 (as CELLCEPT) as antimetabolite immunosuppressant (see Label). Many generics are available. The compound was covered in the US by US4753935 that expired on 05.03.2009 and the crystalline form by US US5543408 that expired on 15.09.2013.

22. steroids [methylprednisolone] (off-label for disease modification, on-label for relapses [please consider off-label])

One of the first scientific publication on the use of methylprednisolone was published in 1996 (Hommes OR, Barkhof F, Jongen PJ, Frequin ST. Methylprednisolone treatment in multiple sclerosis: effect of treatment, pharmacokinetics, future. Mult Scler. 1996 Jul;1(6):327-8. doi: 10.1177/135245859600100607. PMID: 9345410). No related patents found however any "generic" patnete on the use in MS would have expired today. Patents on combinations with other compounds or specific treatment regimen may exist and may still be filed but should only have a limited scope.

Patent information provided on 13.06.2019

23. Azathioprine [original: Imuran®; Sebela Ireland LTD, US 1968]

Description		Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
Azathioprine compound patent	US3056785	80's																

24. Cladribine i.v.

Description		Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
Cladribine product	US4760137	2005																

25. Cyclophosphamide [original: Cytoxan®, Baxter, US 1959]

Description		Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
Product off patent first	-	70's																

Description		Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
approved in the US in the 50's																		

26. Fludarabine [original: Fludara®, Genzyme, US 1991]

Description		Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
Fludarabine compound	US4210745 (filed 1978)	90's																
Fludarabine Phosphate compound (prodrug) derivatives of 9 beta -D-arabinofuranosyl-2-fluoroadenine	US4357324 (filed1982)	2002																

27. Leflunomide [original: Arava®; Sanofi Aventis, US 1998]

Description		Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
Leflunomide compound patent	DE2854439 US4284786 (filed 1976)	90's																

28. Methotrexate

Description		Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
Methotrexate compound	US2512572(filed 1947)	60's																

29. Mitoxantrone

Description		Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
Mitoxantrone compound	DE2835661 US4197249 (filed 1978)	1998																

30. Rituximab [several brand names, Rituxan®]

Rituximab product patents expired between 2015 and 2018. Biosimilar versions of **rituximab** have been approved in numerous countries, including, for example, the European Union, South Korea, Bolivia, Chile, Peru, India, and Australia[1]. Secondary method of use patents concerning rituximab have been filed or granted in some jurisdictions,

[1] Generics and Biosimilars Initiative. Biosimilars of rituximab. http://www.gabionline.net/Biosimilars/General/Biosimilars-of-rituximab

including in China, Malaysia, Mexico, and South Africa (expected to expire in 2019). Apart from these, there do not appear to be active patents covering the intravenous formulation of rituximab.

Secondary formulation patents for a subcutaneous administration form of rituximab (rituximab and hyaluronidase human approved to Genentech in the USA as RITUXAN HYCELA™) have been filed in the majority of LMIC jurisdictions that were surveyed and already granted in China, Morocco, Ukraine and Vietnam (expected to expire in 2030).

In 2005 Genentech filed an international application of a specific treatment regimen of rituximab in MS however patents were not granted or abandoned in view of the prior art create by the Genmab's international patent on ofatumumab and its uses, including in MS (WO2004035607)

Description		Expected date of expiry in LMICs	ARIPO	BRA	CHN	EAPO	GTM	IDN	IND	MAR	OAPI	PHL	THA	UKR	ZA	VNM	US	EP
Product and methods of use	WO 94/11026	2013-18	.	N	N	N	u	.	N	u	u		N	u	N	N	G 2018†	G 19-22
Combination therapies for B Cell Lymphomas using anti Cd20 Antibody	WO 00/09160 A1	2019-2022	.	N	G	G	u	.	.	u	u		G	.	G	.	G	G 19-22
Use in chronic lymphocytic leukemia (CLL)	WO 00/27428 A1	2019	.	G	G	.	u	.	.	u	u		G	u	G	.	G/C	G
Formulation for subcutaneous injection	US 2011/0076273	2030	.	F	G	F	.	F	.	G	.		F	G	F	G	G	F