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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Multiple Sclerosis Agents. [Updated 2022 Sep 7].
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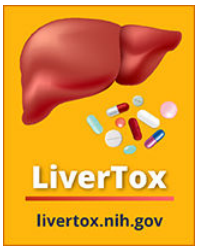

Multiple Sclerosis Agents

Updated: September 7, 2022.

OVERVIEW

Multiple sclerosis is a chronic demyelinating disorder of the central nervous system of unknown etiology. It is most likely caused by a gradual, intermittent autoimmune destruction of myelin. The disorder is characterized by a relapsing-remitting course, but in a small proportion of patients, it is unremittingly progressive even from the onset. The disease typically presents between the ages of 20 and 40 years and is more common in women than men. Rates of multiple sclerosis vary geographically, being highest in Northern parts of Europe and the United States and in Canada. Multiple sclerosis affects an estimated 400,000 persons in the United States and is the most common cause of neurologic disability in young adulthood.

Therapies of multiple sclerosis can be divided into disease modifying agents and symptomatic therapies. The disease modifying agents are largely immunomodulatory drugs including interferon beta-1a (Avonex, 1994 and Rebif, 2003), interferon beta-1b (Betaseron and Extavia, 1993), peginterferon beta-1a (Plegridy, 2014), glatiramer acetate (Copaxone and Glatopa 1996), alemtuzumab (Lemtrada, 2001), natalizumab (Tysabri, 2004), mitoxantrone (generic, 2006), fingolimod (Gilenya, 2010), teriflunomide (Aubagio, 2012), three fumarates (dimethyl fumarate: Tecfidera, 2013; diroximel fumarate: Vumerity, 2019; and monomethyl fumarate: Bafiertam, 2020), ocrelizumab (Ocrevus, 2017), daclizumab (Zinbryta, 2017; withdrawn 2018), cladribine (Mavenclad, 2018), siponimod (Mayzent, 2019), ozanimod (Zeposia, 2020) and Ponesimod (Ponvory, 2021). Disease modifying agents that are used in resistant cases of multiple sclerosis some of which are not specifically approved for this use (off-label use) include methotrexate, cyclophosphamide, and intravenous immunoglobulins. The disease modifying agents are more effective in relapsing-remitting forms of disease than in the more severe and intractable progressive forms. Symptomatic therapies developed for multiple sclerosis include dalfampridine (4-aminopyrine; Ampyra, 2010), a potassium channel blocker that improves mobility and walking speed in patients with relapsing-remitting forms of multiple sclerosis.

While transient, asymptomatic and mild-to-moderate serum aminotransferase elevations occur not uncommonly with most of the drugs used to treat multiple sclerosis, clinically apparent hepatotoxicity is rare. Nevertheless, several convincing instances of acute liver injury have been reported for the various forms of interferon beta, glatiramer acetate, dimethyl fumarate, alemtuzumab, daclizumab, and fingolimod. Importantly, clinically apparent liver injury was usually first attributed to these agents several years after their introduction, and initially they were not believed to be hepatotoxic. Thus, many of the more recently introduced agents (fingolimod, siponimod, ozanimod, ponesimod, teriflunomide, cladribine, and the fumarates) have not had wide enough general use to state that they do not cause clinically apparent liver injury, and all have been associated occasionally with marked but transient increases in serum aminotransferase levels.

The following agents are discussed individually in LiverTox.

DISEASE MODIFYING AGENTS					
Generic Name Brand Name	Type of Agent	Approval for MS	Indication Type of MS	Route and Regimen	Likelihood Score
Alemtuzumab Campath	mAb to CD-52	2001	RRMS, SPMS	iv [3 or 5 days] every 12 months	D
Cladribine Mavenclad	Purine Antimetabolite	2017	RRMS, SPMS	oral daily in two 4- to 5-day courses	E
Daclizumab Zinbryta	mAb to IL2 Receptor	2017 Withdrawn	RRMS	sc once monthly	C
Dimethyl Fumarate Tecfidera	Nrf2 Activator	2013	RRMS, SPMS, CIS	oral twice daily	C
Diroximel Fumarate Vumerity*	Nrf2 Activator	2019	RRMS, SPMS, CIS	oral twice daily	E*
Monomethyl Fumarate Bafiertam*	Nrf2 Activator	2020	RRMS, SPMS, CIS	oral twice daily	E*
Fingolimod Gelenya	S1P Receptor Modulator	2010	RRMS, SPMS, CIS	oral once daily	C
Glatiramer Acetate Glatopa	Amino Acid Polymers	1996	RRMS, SPMS, CIS	sc daily or thrice weekly	B
Interferon beta-1a Avonex, Rebif	Recombinant Cytokine	1996	RRMS, SPMS, CIS	im weekly sc thrice weekly	A
Interferon beta-1b Betaseron, Extavia	Recombinant Cytokine	1993	RRMS, SPMS, CIS	sc every other day	A
Peginterferon beta-1a Plegridy	Pegylated Rec Cytokine	2014	RRMS, SPMS, CIS	sc every 2 weeks	A
Mitoxantrone Generic	Cytotoxic Antibiotic	2006	RRMS, SPMS	iv every 3 months	D
Natalizumab Tysabri	mAb to α4β1 integrin	2005	RRMS, CIS, SPMS	iv every 4 weeks	C
Ocrelizumab Ocrevus	mAb to CD-20	2017	RRMS, CIS, SPMS, PPMS	iv every 6 months	D
Ozanimod Zeposia	S1P Receptor Modulator	2020	RRMS, CIS, SPMS	oral daily	E*
Ponesimod Ponvory	S1P Receptor Modulator	2021	RRMS, CIS, SPMS	oral daily	E*
Siponimod Mayzent	S1P Receptor Modulator	2019	RRMS, CIS, SPMS	oral daily	E*
Teriflunomide Aubagio	Pyrimidine Syn Inhibitor	2012	RRMS, CIS, SPMS	oral daily	D
SYMPTOMATIC THERAPY					
Generic Name Brand Name	Type of Agent	Approval	Indication	Route and Regimen	Likelihood Score
Dalfampridine Ampyra	Pyrimidine Analogue	2010	RRMS	oral twice daily	E*

Abbreviations: CIS, clinically isolated syndrome; mAb, monoclonal antibody; MS, multiple sclerosis; PPMS, primary progressive multiple sclerosis; RRMS, relapsing, remitting multiple sclerosis; S1P, sphingosine-1-phosphate; SPMS, active secondary progressive multiple sclerosis.

Administration Routes: im, intramuscular; iv, intravenous; sc, subcutaneous.

* Described in chapter on Dimethyl Fumarate.

ANNOTATED BIBLIOGRAPHY

References updated: 07 September 2022

Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Textbook of hepatotoxicity published in 1999, the drugs for multiple sclerosis are not discussed, the majority having been developed and introduced into clinical medicine since 1999).

Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013.

(Multi-authored textbook of hepatotoxicity published in 2013 does not discuss the drugs for multiple sclerosis).

Krensky AM, Azzi JR, Hafler DA. Immunotherapy for multiple sclerosis. Immunosuppressants and tolerogens. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 649-51.

(Textbook of pharmacology and therapeutics).

Interferon beta-1B for multiple sclerosis. Med Lett Drugs Ther. 1993;35(900):61–2. PubMed PMID: 8515719.

(Concise review of mechanism of action, efficacy, safety and costs of interferon beta-1b shortly after its approval for use in multiple sclerosis in the US, mentions that it is generally well tolerated; no mention of ALT elevations or hepatotoxicity).

Interferon beta-1A for relapsing multiple sclerosis. Med Lett Drugs Ther. 1996;38(979):63–4. PubMed PMID: 8692073.

(Concise review of efficacy and safety of interferon beta-1a [Avonex] shortly after its approval for multiple sclerosis in the US, mentions side effects of flu-like symptoms, injection site reactions, but does not mention ALT elevations or hepatotoxicity).

Glatiramer acetate for relapsing multiple sclerosis. Med Lett Drugs Ther. 1997;39(1004):61–2. PubMed PMID: 9217693.

(Concise review of mechanism of action, efficacy, safety and costs of glatiramer acetate for relapsing multiple sclerosis shortly after its approval in the US, mentions injection reactions [local and systemic], but that "no hematological or hepatic toxicity has been detected").

Beta interferons for multiple sclerosis. Med Lett Drugs Ther. 2002;44(1141):88–9. PubMed PMID: 12381969.

(Concise review of efficacy, safety and costs of 3 forms of interferon beta for multiple sclerosis mentions that serum enzyme abnormalities were more frequent with Betaseron [beta-1b] and Avonex [beta-1a] than with Rebif [beta-1a], but does not mention clinically apparent liver injury).

Natalizumab (Tysabri) for relapsing multiple sclerosis. Med Lett Drugs Ther. 2005;47(1202):13–5. PubMed PMID: 15711498.

(Concise review of mechanism of action, efficacy, safety and costs of natalizumab [humanized monoclonal antibody to integrin] shortly after its approval for this indication in the US, mentions hypersensitivity reactions and neutralizing antibody, but not ALT elevations or clinically apparent liver injury; this agent was withdrawn from the market one year later because of progressive multifocal leukoencephalopathy [PML]).

Alemtuzumab (Compath) off-label for relapsing multiple sclerosis. Med Lett Drugs Ther. 2009;51(1307):17–8.

(Discussion of the off label use of alemtuzumab [humanized monoclonal antibody to CD52] for relapsing multiple sclerosis, mentions that side effects include infusion reactions, autoimmune thyroid disorders and thrombocytopenic purpura, but does not mention ALT elevations or clinically apparent hepatotoxicity).

Interferon beta-1b (Extavia) for multiple sclerosis. Med Lett Drugs Ther. 2010;52:86–7. PubMed PMID: 21045760.

(Concise review of efficacy and safety of interferon beta-1b [Extavia] shortly after its approval in the US, mentions that hepatic enzyme elevations may occur).

Oral fingolimod (Gilenya) for multiple sclerosis. Med Lett Drugs Ther. 2010;52(1353-1354):98–9. PubMed PMID: 21344782.

(Concise review of mechanism of action, efficacy, safety and costs of fingolimod shortly after is approval for use for multiple sclerosis in the US, mentions that common side effects are headache, cough, diarrhea, back pain and aminotransferase elevations; no mention of clinically apparent liver injury).

Dalfampridine (Ampyra) for MS. Med Lett Drugs Ther. 2010;52(1347):73–4. PubMed PMID: 20847716.

(Concise review of the mechanism of action, efficacy, safety and costs of dalfampridine shortly after its approval in the US, mentions common side effects were urinary tract infection, insomnia, dizziness, headache, nausea, fatigue, back pain and ataxia; no mention of ALT elevations or hepatotoxicity).

Gold R. Oral therapies for multiple sclerosis: a review of agents in phase III development or recently approved. CNS Drugs. 2011;25:37–52. PubMed PMID: 21128693.

(Review of the mechanism of action, efficacy and safety of 5 new, oral therapies of multiple sclerosis, mentions serum enzyme elevations occurring in 8.5-12.5% of fingolimod treated vs 1.7% on placebo, and at an increased rate with teriflunomide).

Killestein J, Rudick RA, Polman CH. Oral treatment for multiple sclerosis. Lancet Neurol. 2011;10:1026–34. PubMed PMID: 22014437.

(Review of the clinical usefulness and safety of 5 new oral therapies for relapsing multiple sclerosis, mentions that liver enzyme elevations can occur with teriflunomide and fingolimod therapy).

New drugs for relapsing multiple sclerosis. Med Lett Drugs Ther. 2012;54(1403):89–91. PubMed PMID: 23183318.

(Concise review of efficacy, safety and costs of new disease modifying drugs for multiple sclerosis lists side effects in a table including "transaminase elevations" for interferon beta, fingolimod and teriflunomide, and "hepatotoxicity" for natalizumab, but not for glatiramer or mitoxantrone).

Dimethyl fumarate (Tecfidera) for multiple sclerosis. Med Lett Drugs Ther. 2013;55(1418):45–7.

(Concise review of mechanism of action, efficacy, safety and costs of dimethyl fumarate for multiple sclerosis shortly after its approval in the US mentions side effects of flushing, abdominal pain, nausea and lymphopenia, but not ALT elevations or hepatotoxicity).

Oh J, O'Connor PW. Safety, tolerability, and efficacy of oral therapies for relapsing-remitting multiple sclerosis. CNS Drugs. 2013;27:591–609. PubMed PMID: 23801528.

(Review of new oral therapies for multiple sclerosis lists elevated serum enzymes as occurring with fingolimod, teriflunomide, dimethyl fumarate and laquinimod).

Peginterferon beta-1a (Plegridy) for multiple sclerosis. Med Lett Drugs Ther. 2015;57(1468):67–9. PubMed PMID: 25941954.

(Concise review of efficacy, safety and costs of peginterferon beta-1a shortly after its approval for use in multiple sclerosis in the US, mentions that injection site reactions and influenza-like symptoms are common adverse effects, but does not mention ALT elevations or hepatotoxicity).

Pawate S, Bagnato F. Newer agents in the treatment of multiple sclerosis. Neurologist. 2015;19:104–17. PubMed PMID: 25888198.

(Summary of the efficacy and safety of new drugs for multiple sclerosis mentions that fingolimod, laquinimod and teriflunomide have been associated with serum enzyme elevations during treatment, but no specifics given).

English C, Aloi JJ. New FDA-approved disease-modifying therapies for multiple sclerosis. Clin Ther. 2015;37:691–715. PubMed PMID: 25846320.

(Systematic review of efficacy and safety of the newer disease modifying therapies of multiple sclerosis, lists ALT elevations as adverse events associated with fingolimod, teriflunomide and dimethyl fumarate, but not peginterferon beta or alemtuzumab).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology. 2015;148:1340–52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 7 [0.8%] were attributed to interferon beta, but none were linked to other drugs used for multiple sclerosis).

Feinstein A, Freeman J, Lo AC. Treatment of progressive multiple sclerosis: what works, what does not, and what is needed. Lancet Neurol. 2015;14:194–207. PubMed PMID: 25772898.

(Commentary on management of progressive multiple sclerosis in which most of the newer disease modifying agents have little effect, stresses that major attention should be paid to management and relief of symptoms such as fatigue, bladder dysfunction, spasticity, pain, depression and cognitive dysfunction; no discussion of liver related adverse effects of medications).

Drugs for multiple sclerosis. Med Lett Drugs Ther. 2016;58(1496):71–4. PubMed PMID: 27249095.

(Concise review of the mechanism of action, clinical efficacy, safety, costs and relative role of the medications approved for use in multiple sclerosis mentions that beta interferon and natalizumab can cause clinically apparent liver injury and that fingolimod and teriflunomide are associated with frequent serum enzyme elevations).

Daclizumab (Zinbryta) for multiple sclerosis. Med Lett Drugs Ther. 2016;58(1503):117–9. PubMed PMID: 27603962.

(Concise review of the mechanism of action, clinical efficacy, safety, and costs of daclizumab shortly after its approval for use in multiple sclerosis mentions that it has many safety concerns and should be reserved for patients who do not respond to first line therapies and that hepatotoxicity, autoimmune reactions and serum aminotransferase elevations are potential adverse events).

Siponimod (Mayzent)--a new drug for multiple sclerosis. Med Lett Drugs Ther. 2019;61(1571):70–2. PubMed PMID: 31169805.

(Concise review of the mechanism of action, clinical efficacy, safety, and costs of siponimod, the second sphingosine-1 receptor modulator approved for use in multiple sclerosis; mentions that it is associated with

serum ALT elevations and patients should have routine liver tests and have CYP 2C9 genotyping before starting).

Cladribine (Mavenclad) for multiple sclerosis. Med Lett Drugs Ther. 2019;61(1577):118–20. PubMed PMID: 31381552.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of cladribine, mentions that patients should be tested for hepatitis B and C before starting cladribine because of concerns over reactivation).

Holmøy T, Fevang B, Olsen DB, Spigset O, Bø L. Adverse events with fatal outcome associated with alemtuzumab treatment in multiple sclerosis. BMC Res Notes. 2019;12:497. PubMed PMID: 31405369.

(Systematic review of fatal adverse events associated with alemtuzumab therapy of multiple sclerosis identified 9 fatal instances one of which was autoimmune hepatitis that arose 15 months after starting therapy).

Butzkueven H, Kappos L, Wiendl H, Trojano M, Spelman T, Chang I, Kasliwal R, et al; Tysabri Observational Program (TOP) Investigators. Long-term safety and effectiveness of natalizumab treatment in clinical practice: 10 years of real-world data from the Tysabri Observational Program (TOP). J Neurol Neurosurg Psychiatry. 2020;91(6):660–8. PubMed PMID: 32234967.

(A long term observational study enrolled 6148 patients from 17 countries with multiple sclerosis as they started natalizumab with follow up for up to 11 years [median=5.2 years]; 829 patients [13.5%] had at least one serious adverse event including progressive multifocal leukoencephalopathy in 53 [0.9%], malignancy in 66 [1.1%] and hepatic events in 12 [0.2%] described as drug induced liver injury in 4, autoimmune hepatitis in 2 and acute liver failure, fulminant hepatitis, hepatitis and liver injury in 1 each: no specific details given).

Ozanimod (Zeposia) for multiple sclerosis. Med Lett Drugs Ther. 2020;62(1605):132–4. PubMed PMID: 32970043.

(Concise review of the mechanism of action, clinical efficacy, toxicity and costs of ozanimod shortly after its approval for use in relapsing multiple sclerosis in the US mentions that ozanimod is associated with ALT and AST elevations and that therapy lowers lymphocyte counts and increases the risk of infections including herpes zoster).

Lu MC, Shih YL, Hsieh TY, Lin JC. Flare of hepatitis B virus after fingolimod treatment for relapsing and remitting multiple sclerosis. J Formos Med Assoc. 2020;119:886–7. PubMed PMID: 31679907.

(Letter describing 41 year old Taiwanese woman with relapsing multiple sclerosis and inactive HBsAg carrier state who developed reactivation of hepatitis B after 35 months of treatment with fingolimod [ALT 385 U/L, HBV DNA 8 log_{10} IU/mL, bilirubin not given], who responded to tenofovir with resolution of ALT elevations and decrease of HBV DNA levels to undetectable despite continuation of fingolimod).

Markham A. Ponesimod: first approval. Drugs. 2021;81:957–62. PubMed PMID: 33939119.

(Review of the mechanism of action, development, clinical efficacy and safety of ponesimod shortly after its approval in the US in 2021, mentions that serum aminotransferase elevations occurred in 23% of ponesimod recipients in one large preregistration trial).

Drugs for multiple sclerosis. Med Lett Drugs Ther. 2021;63(1620):42–8. PubMed PMID: 33976089.

(Concise review of the relative clinical efficacy, safety and costs of drugs for relapsing multiple sclerosis including parenteral agents [such as interferon-beta, glatiramer acetate, natalizumab, alemtuzumab, ocrelizumab, ofatumumab, rituximab and mitoxantrone] and the oral agents [such as the S1P receptor modulators, cladribine, fumarates, and teriflunomide], many of which are associated with serum ALT elevations and several have been reported to cause clinically apparent liver injury or reactivation of hepatitis B).

Biolato M, Bianco A, Lucchini M, Gasbarrini A, Mirabella M, Grieco A. The disease-modifying therapies of relapsing-remitting multiple sclerosis and liver injury: a narrative review. CNS Drugs. 2021;35:861–880. PubMed PMID: 34319570.

(Extensive review of the pre- and postmarketing data on hepatotoxicity of disease modifying therapies of relapsing forms of multiple sclerosis, none of which are completely free of the potential of hepatotoxicity, including interferon beta, glatiramer, fingolimod, teriflunomide, dimethyl fumarate, cladribine, natalizumab, alemtuzumab and ocrelizumab).