Subject: MS treatment and risk of viral infection

Dear Healthcare Professional,

When discussing treatment options with your multiple sclerosis (MS) patients, you or patients may have questions about viral infection risks associated with DMTs. In these occasions, it may be helpful to consider looking across all Summary of Product Characteristics (SPCs) to assess the stated **viral infection risk with DMTs.**

Rebif and interferon beta (preparations) showed no identifiable increased risk of viral infections known at the date of approval.

Viral infection risk with DMTs: summary based on list of adverse reactions included in the SPCs [a,b]

	NO IDENTIFIED RISK	VERY RARE	RARE	UNCOMMON	COMMON	VERY COMMON	FREQUENCY UNKNOWN
IFN β-1b[1]	No identified risk						
IFN β-1b[2]	No identified risk						
Peg-IFN β-1a[3]	No identified risk						
IFN β-1a[4]	No identified risk						
Glatiramer acetate[5]				Herpes zoster	bronchitis, herpes simplex, gastroenteritis	Influenza	
Cladribine[6]					Oral herpes, dermatomal herpes zoster[c]		
Dimethyl fumarate[7]					gastroenteritis		PML, herpes zoster
Fingolimod[8]				pneumonia	Herpes, bronchitis	Influenza, sinusitis	PML, cryptococcal infections
Teriflunomide[9]					Influenza, URTI, bronchitis, sinusitis, pharyngitis, gastroenteritis viral, oral herpes, laryngitis		sepsis
Alemtuzumab[10]				Acute sinusitis, pneumonitis, cytomegalovirus	Herpes zoster, LRTI, gastroenteritis, influenza, pneumonia	URTI, herpes, influenza	Epstein-Barr virus reactivation
Natalizumab[11]				PML		Nasopharyngitis	
Ocrelizumab[12]					Sinusitis, bronchitis, oral herpes, gastroenteritis, RTI, viral infection, herpes zoster	URTI, nasopharyngitis, influenza	

Note! The data presented in the table applies only to viral infections known at the date of approval and does not include any novel viruses identified since the date of approval. Table has been sorted in order of injectable, oral and infusion DMTs.

[a]EU labels accessed Apr 2020; [b]Frequency: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000); [c]The incidence of herpes zoster was higher during the period of grade 3 or 4 lymphopenia (<500 to 200 cells/mm³ or <200 cells/mm³) compared to the time when the patients were not experiencing grade 3 or 4 lymphopenia.

Date of preparation August 2020, UI-REB-00011

IFN=interferon; im=intramuscular; LRTI=lower respiratory tract infections; peg=pegylated; PML=progressive multifocal leukoencephalopathy; URTI=upper respiratory tract infection.

Rebif has a well-established safety profile in MS based on more than 20 years of clinical and real-world experience[13-23] and 1.69 million patient-years of therapy since approval[1,24d]

No increase in viral infections vs no-treatment group, including no cases of PML reported[13-16]

No increased risk of serious infections vs no-treatment group[13-16]

No increased risk of malignancy vs no-treatment group[20]

Approved for use during pregnancy if clinically needed and during breastfeeding[1e]

PML=progressive multifocal leukoencephalopathy.

[d]As of September 2019.
[e]Experience with exposure during the second and third trimester is very limited.

Please see Prescribing Information below for additional information.

Kind regards and stay safe,

Neurology & Immunology Team

Merck UK and Republic of Ireland

References:

1. Rebif® SmPC, Jan 2020. **2.** IFN β-1b SmPC, Oct 2019. **3.** Peg-IFN β-1a SmPC, Oct 2019. **4.** im IFN β-1a SmPC, Oct 2019. **5.** Glatiramer acetate UK SmPC, Oct 2019. **6.** MAVENCLAD® SmPC, Jan 2020. **7.** Dimethyl fumarate SmPC, Jan 2020. **8.** Fingolimod SmPC, Dec 2019. **9.** Teriflunomide SmPC, Feb 2020. **10.** Alemtuzumab SmPC, Jan 2020. **11.** Natalizumab SmPC, Nov 2019. **12.** Ocrelizumab SmPC, Jan 2018. **13.** PRISMS Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. *Lancet.* 1998;352(9139):1498–1504. **14.** PRISMS Study Group and the University of British Columbia MS/MRI Analysis Group. PRISMS-4: long-term efficacy of interferon-beta-1a in relapsing MS. *Neurology.* 2001;56(12):1628–1636. **15.** Kappos L, Polman CH, Freedman MS, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. *Neurology.* 2006;67(7):1242-1249. **16.** Kappos L, Kuhle J, Multanen J. Factors influencing long-term outcomes in relapsing-remitting multiple sclerosis: PRISMS-15. *J Neurol Neurosurg Psychiatry*. 2015;86(11):1202–1207. **17.** Harty G, Wong SL, Gillett A, Davies A. Subcutaneous Interferon beta-1a, 10-Year Results from the United Kingdom Multiple Sclerosis Risk Sharing Scheme. Presented at: ECTRIMS 2018; October 10-12, 2018. Berlin, Germany. P914. **18.** Winkelmann A, Loebermann M, Reisinger EC, Hartung HP, Zettl UK. Disease-modifying therapies and infectious risks in multiple sclerosis. *Nat Rev Neurol.* 2016;12(4):217–233. **19.** Winkelmann A, Loebermann M, Reisinger EC, Zettl UK. Multiple sclerosis treatment

and infectious issues: update 2013. *Clin Exp Immunol*. 2014;175(3):425–438. **20.** Sandberg-Wollheim M, Kornmann G, Bischof D, Moraga MS, Hennessy B, Alteri E. The risk of malignancy is not increased in patients with multiple sclerosis treated with subcutaneous interferon beta-1a: Analysis of data from clinical trial and post-marketing surveillance settings. *Mult Scler.* 2011;17(4):431–440. **21.** Hellwig K, Geissbuehler Y, Sabido M, et al. Pregnancy and infant outcomes with interferon beta: data from the European interferon beta pregnancy registry and population-based registries in Finland and Sweden. Presented at: ECTRIMS 2018; October 10-12, 2018. Berlin, Germany. P1753. **22.** Hellwig K, Geissbuehler Y, Sabido M, et al. Pregnancy outcomes in interferon-beta-exposed patients with multiple sclerosis: results from the European interferon-beta pregnancy registry. *J Neurol.* 2020;267(6):1715-1723. **23.** Thiel S, Langer-Gould A, Rockhoff M, et al. Interferon-beta exposure during first trimester is safe in women with multiple sclerosis—a prospective cohort study from the German multiple sclerosis and pregnancy registry. *Mult Scler.* 2016;22(6):801–809. **24.** Periodic Benefit Risk Evaluation Report for Rebif, September 2019.

PRESCRIBING INFORMATION – UK AND IRELAND

REBIF (Interferon beta-1a) (Please refer to the full Summary of Product Characteristics before prescribing)

PRESENTATION: Pre-filled glass syringes containing 8.8 µg/0.2 ml, 22 µg/0.5 ml, 44 µg/0.5 ml Rebif solution. Disposable pre-filled pen injector (RebiDose) containing 8.8 µg/0.2 ml, 22 µg/0.5 ml, 44 µg/0.5 ml Rebif solution. Pre-filled glass cartridges containing 22 µg/0.5 ml, 44 µg/0.5 ml, 8.8 µg/0.1 ml and 22 µg/0.25 ml Rebif cartridges.
INDICATIONS: For treatment of :
• patients with a single demyelinating event with an active inflammatory process, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis.
N.B. Rebif 22 µg presentations are not indicated in the treatment of single clinical events suggestive of multiple sclerosis.
• patients with relapsing multiple sclerosis. In clinical trials, this was characterised by two or more acute exacerbations in the previous two years.
DOSAGE AND ADMINISTRATION: Initiate under supervision of a physician experienced in the treatment of multiple sclerosis. Administer by subcutaneous injection.
Dose: Weeks 1 and 2: 8.8 µg three times per week (TIW); weeks 3 and 4: 22 µg TIW; week 5 onwards: 44 µg TIW (22 µg TIW can be used if patients cannot tolerate higher dose, but only in treatment of relapsing multiple sclerosis). Do not use in patients under 2 years of age. Prior to injection and for an additional 24 h after each injection, an antipyretic analgesic is advised. Evaluate patients at least every second year of the treatment period.
CONTRAINDICATIONS: Hypersensitivity to natural or recombinant interferon-beta, or to any of the excipients; current severe depression and/or suicidal ideation.
PRECAUTIONS: Use with caution in patients: with previous or current depressive disorders and those with antecedents of suicidal ideation; with a history of seizures or those receiving treatment with anti-epileptics, particularly if epilepsy is not controlled; with a history of significant liver disease, active liver disease, alcohol abuse or increased serum ALT; severe renal and hepatic failure or severe myelosuppression; receiving medicines with a narrow therapeutic index cleared by cytochrome P450.
Monitor: patients exhibiting depression and treat appropriately; patients with cardiac disease for worsening of their condition during initiation; serum ALT prior to start of therapy, at months 1, 3 and 6 and periodically thereafter - stop treatment if icterus or symptoms of liver dysfunction appear. Treatment has potential to cause severe liver injury including acute hepatic failure; patients with severe renal and hepatic failure or severe myelosuppression; haematological parameters at months 1, 3 and 6 and periodically thereafter; early signs and
symptoms of nephrotic syndrome especially in patients at higher risk of renal disease. All monitoring should be more frequent when initiating Rebif 44.
Cases of thrombotic microangiopathy (TMA) have been reported. If clinical features are observed, testing of platelet levels, serum LDH, blood films and renal function is recommended. If TMA is diagnosed, treat promptly. Immediate discontinuation of Rebif is recommended. Cases of nephrotic syndrome have been reported during treatment with interferon-beta products. Prompt treatment of nephrotic syndrome is required and discontinuation of Rebif should be considered. New or worsening thyroid abnormalities may occur. Thyroid function testing is recommended at baseline and if abnormal, every 6 – 12 months.
Serum neutralising antibodies may develop and are associated with reduced efficacy. If a patient responds poorly to therapy and has neutralising antibodies, reassess treatment.
If clinically needed, Rebif may be considered during pregnancy. Animal data suggest possible increased risk of spontaneous abortion – the risk in pregnant women exposed to interferon beta cannot adequately be evaluated, but the data do not suggest an increased risk so far. Rebif can be used during breast-feeding. If overdose occurs, hospitalise patient and give supportive treatment.
SIDE EFFECTS: In the case of severe or persistent undesirable effects, consider temporarily lowering or interrupting dose. **Very common**: flu-like symptoms, injection site inflammation/reaction, headache, asymptomatic transaminase increase, neutropenia, lymphopenia, leukopenia, thrombocytopenia, anaemia. **Common**: injection site pain, myalgia, arthralgia, fatigue, rigors, fever, pruritus, rash, erythematous/maculo-papular rash, alopecia, diarrhoea, vomiting, nausea, depression, insomnia, severe elevations of transaminases. **Other side effects include**: injection site necrosis/abscess/infections/cellulitis, panniculitis (in the injection site), urticaria, thyroid dysfunction, hepatic failure, hepatitis with or without icterus, autoimmune hepatitis, anaphylactic

reactions, angio-edema, erythema multiforme, erythema multiforme-like skin reactions, drug-induced lupus erythematosus, nephrotic syndrome, glomerulosclerosis, seizures, transient neurological symptoms, thromboembolic events, TMA including thrombotic thrombocytopenic purpura/haemolytic uremic syndrome, pancytopenia, suicide attempt, Stevens-Johnson syndrome, dyspnoea, pulmonary arterial hypertension, retinal vascular disorders.

Prescribers should consult the Summary of Product Characteristics in relation to other side effects.

LEGAL CATEGORY: POM.

PRICE:
Rebif 8.8 µg and 22 µg: 6 (0.2 ml) + 6 (0.5 ml) syringes/pens - £552.19
Rebif 8.8 µg/0.1 ml and 22 µg/0.25 ml: 2x 1.5 ml cartridges – £406.61
Rebif 22 µg: 12x 0.5 ml syringes/12x0.5 ml pens/4x 1.5 ml cartridges - £613.52
Rebif 44 µg: 12 x0.5 ml syringes/12 x 0.5 ml pens/4 x1.5 ml cartridges - £813.21
For prices in Ireland, consult distributors Allphar Services Ltd.

Marketing Authorisation Holder and Numbers:
Merck Europe B.V., Gustav Mahlerplein 102, 1082 MA Amsterdam, The Netherlands; EU/1/98/063/007; 003 ; 006 ; 017; 013 ; 016 ; 010 ; 008 ; 009.
For further information contact:
UK: Merck Serono Ltd, 5 New Square, Bedfont Lakes Business Park, Feltham, Middlesex, TW14 8HA. Tel: 020 8818 7373.
Republic of Ireland: Merck Serono, 4045 Kingswood Road, Citywest Business Campus, Dublin 24. Tel: 01 4687590.

Date of Preparation: January 2020 **Job No**: UK&IE/REB/0718/0011(2)

PRESCRIBING INFORMATION – UK AND IRELAND

MAVENCLAD (cladribine) (Please refer to the full Summary of Product Characteristics before prescribing)

PRESENTATION: Cartons of 1, 4 or 6 tablets. Each tablet contains 10 mg of cladribine.
INDICATIONS: Treatment of adults with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features.
DOSAGE AND ADMINISTRATION: Must be initiated and supervised by a physician experienced in MS treatment. Recommended cumulative dose: 3.5 mg/kg body weight over 2 years, administered as one treatment course of 1.75 mg/kg per year. Each course comprises 2 treatment weeks, one at the start of the first month and one at the start of the second month of each year. Each treatment week comprises 4 or 5 days on which the patient receives 10 mg or 20 mg as a single daily dose, depending on body weight. For details, see dosage tables in the SPC. No further cladribine treatment is required in years 3 and 4.
CONTRAINDICATIONS: Hypersensitivity to cladribine or to the excipients; HIV infection; active chronic infection (tuberculosis or hepatitis); initiation in immunocompromised patients including those receiving immunosuppressive or myelosuppressive therapy; active malignancy; moderate or severe renal impairment (creatinine clearance <60 mL/min); pregnancy and breast-feeding.
PRECAUTIONS: Not recommended in moderate or severe hepatic impairment. Exercise caution in elderly patients. Determine lymphocyte counts before initiation in years 1 and 2, 2 and 6 months after treatment start in each treatment year. Count should be normal pretreatment in year 1. If count below 500 cells/mm3 at 2 or 6 months, actively monitor until values increase. If count below 800 cells/mm3 pretreatment in year 2, delay treatment. Stop treatment if recovery takes more than 6 months. Screen for latent infections prior to initiation in years 1 and 2. Delay initiation in latent or acute infection until treated. Varicella zoster vaccination is recommended in antibody-negative patients prior to treatment initiation. Delay initiation for 4-6 weeks following vaccination. Consider anti-herpes prophylaxis during grade 4 lymphopenia. If lymphocyte count falls below 500 cells/mm3, actively monitor for symptoms suggestive of infection and initiate anti-infective treatment accordingly. Interrupt
or delay MAVENCLAD until infection has resolved. Perform baseline MRI before initiating MAVENCLAD (usually within 3 months). Evaluate benefit-risk prior to initiation in patients with previous malignancy. Advise patients to follow standard cancer screening guidelines. Exclude pregnancy before initiation in years 1 and 2. Before initiation in year 1 and 2, counsel male and female patients on potential for risk to the foetus and need for effective contraception. Contraception should be used by both male and female patients during treatment and for at least 6 months after the last dose. Women using systemically acting hormonal contraception should add barrier method during treatment and for at least 4 weeks after last dose in each treatment year. In patients previously treated with immunomodulatory or immunosuppressive products, consider their mode of action and duration of effect before initiation of MAVENCLAD. Consider an additive effect on the immune system when such products are used after treatment with MAVENCLAD. When switching from another MS agent, perform a baseline MRI. In patients requiring blood transfusion, irradiation of cellular blood components is recommended prior to administration. Separate administration of any other oral medicinal product by at least three hours from MAVENCLAD administration. Concomitant treatment with other disease-modifying

treatments for MS not recommended. Monitor haematological parameters when taken with other substances that affect the haematological profile. Do not initiate treatment within 4-6 weeks of live or attenuated live vaccines. Avoid vaccines during and after treatment while white blood cells not within normal limits. Avoid co administration of ENT1, CNT3 or BCRP inhibitors during the 4-5 day treatment period. Consider possible decrease in cladribine exposure if potent BCRP or P-gp transporter inducers are co-administered.
SIDE EFFECTS: Very common: Lymphopenia Common: Oral herpes, dermatomal herpes zoster, decreased neutrophils, rash, alopecia Other side effects: Tuberculosis. In clinical studies and long-term follow-up, malignancies were observed more frequently in cladribine-treated patients compared to placebo.

Prescribers should consult the Summary of Product Characteristics in relation to other side effects.

LEGAL CATEGORY: POM.
PRICE:
Pack of 1 tablet: £2,047.24
Pack of 4 tablets: £8,188.97
Pack of 6 tablets: £12,283.46
For prices in Ireland, consult distributor Allphar Services Ltd.

Marketing Authorisation Holder and Numbers:
Merck Europe B.V., Gustav Mahlerplein 102,1082 MA Amsterdam, The Netherlands; EU/1/17/1212/001, 002 & 004

For further information contact:
UK: Merck Serono Ltd, 5 New Square, Bedfont Lakes Business Park, Feltham, Middlesex, TW14 8HA. Tel: 020 8818 7373.
Republic of Ireland: Merck Serono (Ireland) Limited, 4045 Kingswood Road, Citywest Business Campus, Dublin 24. Tel: 01 4687590.

Date of Preparation: January 2020 **Job No:** UK&IE/CLA/0818/0089(2)

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard . In the Republic of Ireland information can be found at www.hpra.ie. Adverse events should also be reported to Merck Serono Limited - Tel: +44(0)20 8818 7373 or email: medinfo.uk@merckgroup.com.