
MERCK
“I AM A WOMAN I HAVE MS
I AM A MOTHER”
Rebif® (interferon beta-1a)
EXPERIENCE NEVER STOPS
MS, multiple sclerosis; RMS, relapsing multiple sclerosis
UK&IE/REB/1019/0015a | March 2020

MS, multiple sclerosis; RMS, relapsing multiple sclerosis

Rebif (interferon beta-1a) is indicated for the 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 MS, and patients with RMS; in clinical trials this was characterized by two or more acute exacerbations in the previous two years[1]

REFERENCES

1. Rebif SmPC, 2020.
2. Zīle I *et al. Cent Eur J Public Health.* 2014;22:147-152.
3. New York State Department of Health. Congenital Malformations Registry Summary Report. 2005.
4. Hellwig K *et al. ECTRIMS* 2018; [A-0950-0000-02658].
5. Buss L *et al. Acta Obstet Gynecol Scand* 2006;85(4):467-75.
6. Hale TW *et al. Breastfeed Med* 2012; 7:123–126.
7. Almas S *et al. Mult Scler Int* 2016;2016:6527458.
8. Avonex SmPC, 2020.
9. Aubagio SmPC, 2020.
10. Copaxone SmPC, 2020.
11. Gilenya SmPC, 2020.
12. Lemtrada SmPC, 2020.
13. **MAVENCLAD®** SmPC, 2020.
14. Ocrevus SmPC, 2020.
15. Tecfidera SmPC, 2020.
16. Tysabri SmPC, 2020.
17. De Stefano N *et al. J Neurol Sci* 2012; 312:97–101.
18. De Stefano N *et al. Mult Scler* 2010; 16:888–892.
19. Panitch H *et al. Neurology* 2002;59:1496–1506.
20. Kappos L *et al. J Neurol Neurosurg Psychiatry* 2015; 86:1202–1207.
21. PRISMS Study Group. *Lancet* 1998; 353:1498–1504.
22. PRISMS Study Group and the University of British Columbia MS/MRI Analysis Group. *Neurology* 2001; 56:1628–1636.
23. Kappos L *et al. Neurology* 2006; 67:944–953.
24. Schwid SR *et al. Clin Ther* 2007; 29:2031–2048.
25. Sandberg-Wollheim M *et al. Mult Scler J* 2011; 17:431–440.
26. Winkelmann A *et al. Nat Rev Neurol* 2016; 12:217–233.
27. Winkelmann A *et al. Clin Exp Immunol* 2014; 175:425–438.
28. Data on file, February 2020
29 Hellwig K *et al. AAN* 2018; [P357].
30. Thiel S *et al. Mult Scler* 2016; 22:801–809.
31. Harty G *et al. ECTRIMS* 2018; [P914].
32. Devonshire VA *et al. BMC Res Notes* 2016; 9:148.
33. Wray S *et al. Expert Opin Drug Deliv* 2018; 15:127–135.
34. Rieckmann P *et al. Adv Ther* 2018; 36:175–186.
35 Verdun di Cantogno E *et al. Patient Prefer Adherence* 2011; 5:173–180.
36. Fernandez O *et al. PLoS One* 2016;11e0160313.

Rebif (interferon beta-1a) may now be considered for the treatment of RMS during pregnancy and breast-feeding

I AM A MOTHER”

Rebif® (interferon beta-1a) | *EXPERIENCE NEVER STOPS*

MS, multiple sclerosis; RMS, relapsing multiple sclerosis
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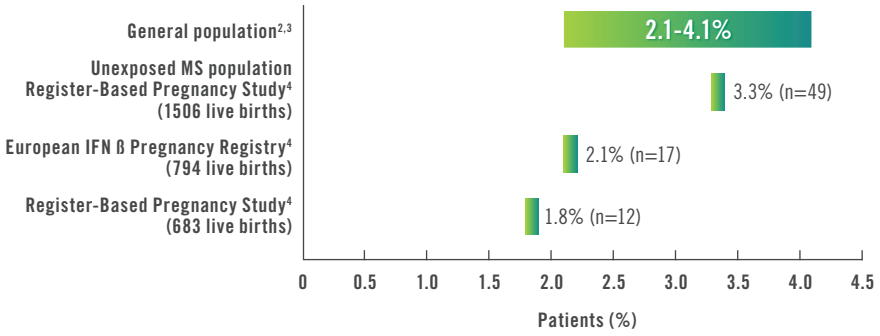
Rebif® can now support RMS patients through their family planning journey[1]

Pregnancy

Rebif may be considered for use during pregnancy, if clinically needed.

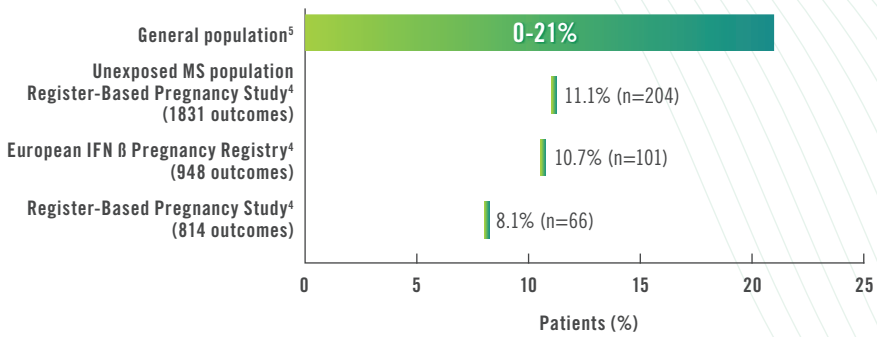
A large amount of data (more than 1,000 pregnancy outcomes) from registries and post-marketing experience indicates no increased risk of major congenital anomalies after pre-conception exposure to interferon beta or such exposure during the first trimester of pregnancy.
However, the duration of exposure during the first trimester is uncertain, because data was collected when interferon beta use was contraindicated during pregnancy, and treatment likely interrupted when the pregnancy was detected and/or confirmed. Experience with exposure during the second and third trimester is very limited.

Congenital malformations following exposure to IFN ß during pregnancy



Based on animal data, there is a possible increased risk for spontaneous abortion. The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot adequately be evaluated based on the currently available data, but the data does not suggest an increased risk so far.

Spontaneous abortions following exposure to IFN ß during pregnancy

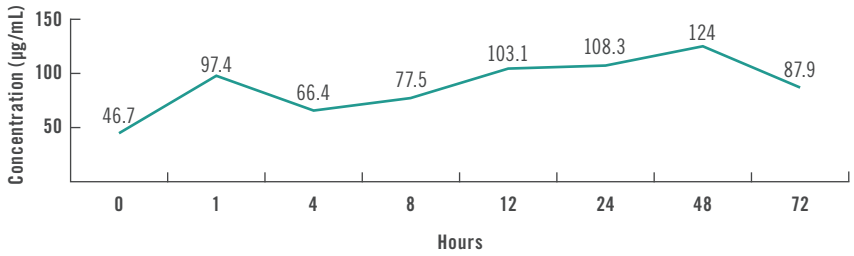


Breast-feeding

Rebif can be used during breast-feeding.

Limited information available on the transfer of interferon beta-1a into breast milk, together with the chemical/physiological characteristics of interferon beta, suggests that levels of interferon beta-1a excreted in human milk are negligible. No harmful effects on the breastfed newborn/infant are anticipated.

IFNs do not readily transfer into breast milk because they are large (22,500 Da), polar molecules highly bound to T lymphocytes and other immune cells[6,7]



Average concentration in breast milk in six mothers treated with intramuscular IFN ß-1a 30µg once weekly. Using the highest values measured (179 µg/mL), the estimated relative infant dose was 0.006% of the maternal dose.
No adverse effects were observed in the breastfed infants.

IFN, interferon; MS, multiple sclerosis; RMS, relapsing multiple sclerosis

Rebif® may be considered during pregnancy and breast-feeding as opposed to most other DMTs[1,8–16]

DMT	SmPC recommendation for pregnancy	SmPC recommendation on lactation
Rebif[1] **and other IFN ß-1**[8]	A large amount of data from registries and postmarketing experience indicates no increased risk of major congenital anomalies after pre-conception exposure to interferon beta or such exposure during the first trimester of pregnancy May be considered during pregnancy, if clinically needed	Limited information suggests levels of IFN ß-1a excreted in human breast milk are negligible. No harmful effects on breastfed infants are anticipated Rebif can be used during breast-feeding
Teriflunomide[9]	Contraindicated during pregnancy	Contraindicated during breast-feeding
Glatiramer acetate[10]	As a precautionary measure, it is preferable to avoid during pregnancy unless the benefit to the mother outweighs the risk to the foetus	A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman
Fingolimod[11]	Contraindicated during pregnancy	Due to the potential for serious adverse reactions to fingolimod in nursing infants, women receiving fingolimod should not breastfeed
Alemtuzumab[12]	Should be administered during pregnancy only if the potential benefit justifies the potential risk to the foetus	A risk to the suckling newborn/infant cannot be excluded. Breast-feeding should be discontinued during each course of treatment and for 4 months following the last infusion of each treatment course. However, benefits of conferred immunity through breast-milk may outweigh the risks of potential exposure to alemtuzumab for the suckling newborn/infant
Cladribine (tablet)[13]	Contraindicated during pregnancy	Breast-feeding is contraindicated during treatment with cladribine (tablet) and for 1 week after the last dose
Ocrelizumab[14]	Should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus	A risk to neonates and infants cannot be excluded. Women should be advised to discontinue breast-feeding during therapy
Dimethyl fumarate[15]	Not recommended during pregnancy and in women of childbearing potential not using appropriate contraception. Should be used during pregnancy only if clearly needed and if the potential benefit justifies the potential risk to the foetus	A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue therapy. The benefit of breast-feeding for the child and the benefit of therapy for the woman should be taken into account
Natalizumab[16]	If a woman becomes pregnant while taking natalizumab, discontinuation of the treatment should be considered. A benefit-risk evaluation of the treatment during pregnancy should take into account the patient's clinical condition and the possible return of disease activity after stopping the medicinal product	The effect of on newborn/infants is unknown. Breast-feeding should be discontinued during treatment

DMD, disease-modifying drug; IFN, interferon

SmPC information correct as of February 2020

Rebif® can support RMS patients through the different phases of family planning[1]

Patients who are currently on **Rebif** may continue treatment throughout their family planning journey if clinically needed

Newly diagnosed	Planning pregnancy	Pregnant	Postpartum (breast-feeding)	Postpartum (not breast-feeding)

- Patients who may plan to have children in the near future
- Patients who are on a DMT not indicated for use during pregnancy
- Patients may continue taking Rebif if pregnancy occurs
- Patients who want to breast-feed and be on treatment

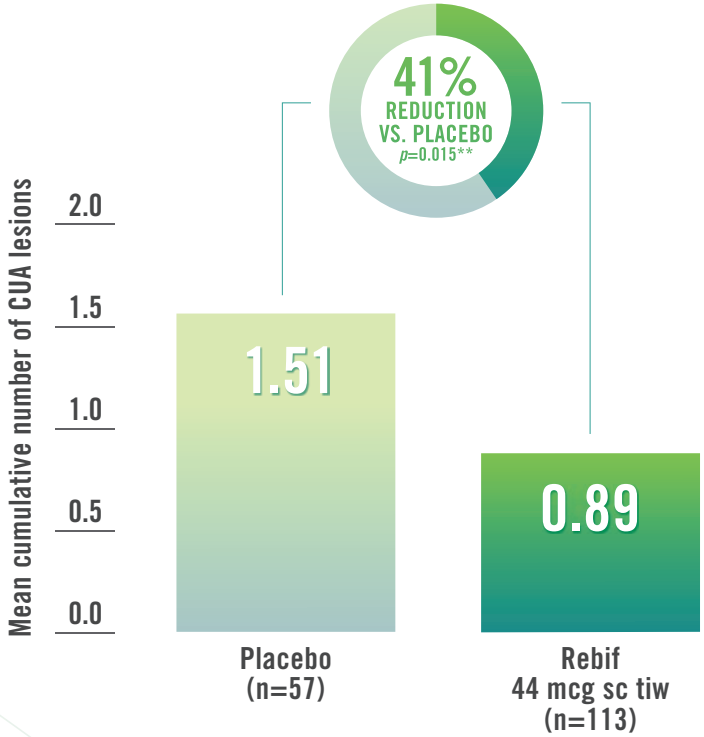
DMT, disease-modifying therapy; RMS, relapsing multiple sclerosis

Rebif®: more than 20 years of clinical and real-world experience[1,17–23]

Rapid onset of action on MRI[17,18]

Rebif has an impact on MRI as early as 4 weeks*[17,18]

IMPROVE study: mean cumulative number of CUA lesions at 4 weeks (*post hoc* analysis)[18]



CUA, combined unique active; IFN, interferon; MRI, magnetic resonance imaging; sc, subcutaneous; tiw, three times weekly

IMPROVE study: A 40-week, randomized controlled trial evaluating the efficacy of a new formulation of sc IFN ß-1a in relapsing-remitting multiple sclerosis. Patients (n = 180) were randomized (2:1) to IFN ß-1a or placebo for 16 weeks; all patients then received IFN ß-1a for 24 weeks. Monthly brain MRI was performed. The primary endpoint was the number of CUA MRI brain lesions at Week 16 in the IFN ß-1a group compared with the placebo group, using the baseline MRI scan as reference

* *Post hoc* analysis. Conventional brain MRI scans were obtained at baseline and every 4 weeks[17,18]
**p values were generated using generalized score tests[18]

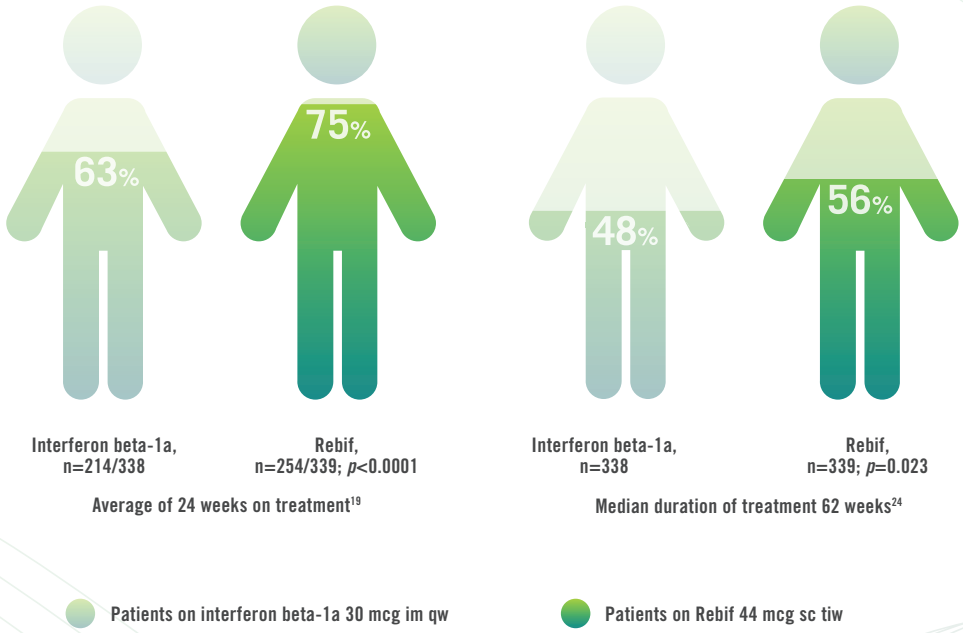
Rebif®: more than 20 years of clinical and real-world experience[1,17–23]

RISK OF RELAPSE ↓

Rebif patients were more likely to remain relapse-free* vs. one weekly intramuscular IFN ß-1a[19]

High-dose, high-frequency Rebif reduced the risk of relapse vs. one weekly intramuscular IFN ß-1a[19,24]

Results from the EVIDENCE study—percentage of patients that remained relapse free:



IFN, interferon; im, intramuscular; MRI, magnetic resonance imaging; qw, once weekly; sc, subcutaneous; tiw, three times weekly

EVIDENCE - Evidence of Interferon Dose-response: European North American Comparative Efficacy
*At 24 and 62 weeks

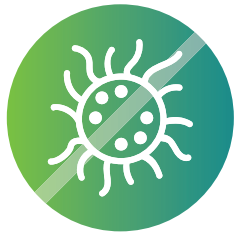
Rebif®: more than 20 years of clinical and real-world experience[1,17–23]

Well-established safety profile based on 20 years of data[1,20-23,25]

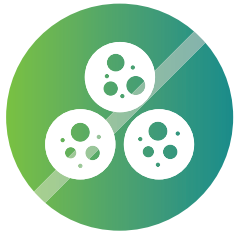
Rebif® has a well-established, long-term safety profile based on 20-year data[1,25-27]

Across many years, Rebif has demonstrated:

No reported cases of PML[28]



No increased risk of serious infections[26,27]



No increased risk of malignancy[25]

No increased risk on pregnancy outcomes*[1,4,29,30]

1,616,700 patient-years of therapy since approval**[31]

IFN, interferon; PML, progressive multifocal leukoencephalopathy; sc, subcutaneous

*Safety profile is obtained from registry data on the use of IFN ß during conception and pregnancy and is not specific to Rebif (IFN ß-1a sc)[2-4]
**In the European post-marketing setting to 03 May 2018

Rebif®: more than 20 years of clinical and real-world experience[1,17–23]

Devices to aid injection convenience[32,33]

Convenient injection experience with RebiSmart®[32]

Patients highly favoured RebiSmart handling, comfort and convenience*[34]

Ready-to-use cartridge[1]

No mixing required[1]

Multi-dose: one cartridge per week[32,34]

Syringe-free injection[1]

Tailored comfort settings[32,35]

Hidden needle[32]

Adjustable depth and speed[32,35]

Treatment and rotation reminders[32,34]

>90% adherence** with RebiSmart over 3 years, for patients who completed the 3-year follow-up n=258[36]

*In a non-interventional, single-arm, 2-year study in patients using RebiSmart, patients rated RebiSmart features out of 10 for first impressions and final thoughts (RebiSmart device version 1.5, with reminder function)[34]

**Adherence by 3-month periods in patients using RebiSmart, from a retrospective, multicenter, observational study. Adherence was measured from the start of treatment to the time of device replacement or treatment discontinuation and was quantified by using the data (dosage, time, and date) automatically recorded by RebiSmart[36]

"I AM A WOMAN I HAVE MS *I AM A MOTHER"*

Talk to your patients to explain how Rebif can now support them through their family planning journey

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)

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.

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 pre-treatment 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

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

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