News Release

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Merck KGaA, Darmstadt, Germany, to Showcase Scientific Leadership at ECTRIMS 2019 with New Data Across Multiple Sclerosis Medicines

- **Company to present 39 abstracts, including data on MAVENCLAD® (cladribine) tablets, Rebif® (interferon beta-1a) and investigational evobrutinib**
- **Long-term data and real-world evidence further characterize effectiveness of MAVENCLAD and support clinical trial findings**

Darmstadt, Germany, August 28, 2019 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced that it will present data on its approved and investigational multiple sclerosis (MS) treatments at the 35th Congress of the European Committee for Treatment and Research In Multiple Sclerosis (ECTRIMS). During ECTRIMS, taking place from 11-13 September 2019, in Stockholm, Sweden, Merck KGaA, Darmstadt, Germany, will present 39 abstracts, including new long-term safety and efficacy data on MAVENCLAD® (cladribine) tablets and new long-term efficacy data for interferon beta (IFN β) therapies, including Rebif® (interferon beta-1a). Data will also be presented further elucidating the proposed mechanism of action for investigational therapy evobrutinib, the first oral, highly selective Bruton's Tyrosine Kinase (BTK) inhibitor to demonstrate clinical proof of concept in relapsing multiple sclerosis (RMS).

"The new data we will be sharing at ECTRIMS touch on several important topics for the scientific community, including long-term safety and efficacy data for MAVENCLAD, long-term efficacy data for interferon beta therapies, including Rebif, and data further elucidating evobrutinib's proposed unique mechanism of action and its potential as a novel therapeutic approach in MS," said Luciano Rossetti, Head of Global R&D for the Biopharma business of Merck KGaA, Darmstadt, Germany. "These data reinforce the important role of our currently-available treatments and

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offer further insights on our investigational treatment, as we continue our unwavering commitment to address the needs of the MS community."

Key MAVENCLAD data include:

- A *post hoc* analysis evaluating five-year disease stability in patients enrolled in the CLARITY and CLARITY EXTENSION trials
- Results from an exploratory analysis of real-world data from an Italian MS registry assessing time-to-treatment change after MAVENCLAD, which examined efficacy of MAVENCLAD on relapse rate and disability progression at five years after starting treatment
- Results from up to 10 years of follow-up from the PREMIERE safety registry, which further support the long-term benefit-risk profile of MAVENCLAD
- New data further illustrating how MAVENCLAD is thought to preferentially target key immune cells involved with MS and its potential qualitative effect on the immune system

Key Rebif data include:

- Results using a new *post hoc* exploratory statistical methodology, which examined changes in disability status over time using eight years of data from the PRISMS study

Key evobrutinib data include:

- Three analyses that investigate the potential role of evobrutinib, the first oral, highly selective BTK inhibitor to demonstrate clinical proof of concept in RMS, in inhibiting pathogenic B-cells and promoting myelin repair

Additional Merck KGaA, Darmstadt, Germany, activities at ECTRIMS 2019:

- Panel discussion and networking event on 11 September bringing together Patient Advocacy Groups, people living with MS and multi-disciplinary experts to have a conversation about family planning with MS (18:00 – 19:30, Epicenter, Stockholm)
- Daily "Meet the Expert" sessions at Merck KGaA, Darmstadt, Germany, booth B40 where different MS experts will share insights from clinical practice with MAVENCLAD, explore family planning for patients with MS and the

company`s ongoing commitment to MS research and development through the Grant for Multiple Sclerosis Innovation (GMSI)

- Satellite symposium events on 11 September (12:30 – 13:30, Hall A Stockholmsmässan) and 12 September (18:15 – 19:15, Hall A Stockholmsmässan) covering key learnings on managing disease progression in MS, including monitoring methods, recent advancements in MS immune targeting and the importance of innovative registry studies
- #MSInsideOut Experience, including the MS House and virtual reality (VR), at Merck KGaA, Darmstadt, Germany, booth B40 that will immerse visitors into a day-in-the-life of an MS patient, educating them on symptoms of MS and how they affect the human body in different settings

Below is a selection of abstracts that have been accepted for presentation at ECTRIMS 2019:

MAVENCLAD® (cladribine) tablets Presentations			
Title	**Authors**	**Abstract No. / Poster No.**	**Presentation Date/Time/Session**
Reduction of risk of secondary progressive multiple sclerosis within two years of treatment with Cladribine Tablets: An analysis of the CLARITY study	Vermersch P, Giovannoni G, Soelberg-Sorensen P, Rammohan K, Cook S, Keller B, Roy S	A-1026-0005-00522	Session Title: Poster Session 1 Session Date: 11.09.2019 Presenting Time: 17:15-19:15 h.
Long-term disease stability assessed by the Expanded Disability Status Scale in patients treated with Cladribine Tablets in the CLARITY and CLARITY Extension studies	Giovannoni G, Comi G, Rammohan K, Rieckmann P, Vermersch P, Dangond F, Keller B, Jack D	A-1026-0033-00521	ePoster
The CLARITY Study: Efficacy Outcomes Among Patients Who Received Disease-Modifying Therapies Prior to Treatment with Cladribine Tablets	Vermersch P, Rammohan K, Damian D, Jack D, Harty G, Wong S L	A-1026-0031-01868	Session Title: Poster Session 1 Session Date: 11.09.2019 Presenting Time: 17:15-19:15 h.

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Updated safety of cladribine tablets in the treatment of patients with multiple sclerosis: Integrated safety analysis and post-approval data	Cook S, Giovannoni G, Leist T, Comi G, Syed S, Nolting A, Damian D, Schick R	A-1026-0033-00523	Session Title: Poster Session 3 Session Date: 13.09.2019 Presenting Time: 12:15-14:15 h.
An analysis of the relationship between cladribine dose and risk of malignancies in patients with multiple sclerosis	Cook S, Giovannoni G, Leist T, Comi G, Nolting A, Sylvester E, Jack D, Damian D, Galazka A	A-1026-0033-01927	Session Title: Poster Session 1 Session Date: 11.09.2019 Presenting Time: 17:15-19:15 h.
Long term, registry-based, prospective, post-authorization safety study evaluating adverse events of special interest in patients with highly active relapsing multiple sclerosis newly started on oral cladribine – CLARION	Butzkueven H, Korhonen P, Hillert J, Trojano M, Aydemir A, Magyari M, Khanfir H, Pinuaga C, Sabidó M, CLARION Study group	A-1026-0033-00518	ePoster
Incidence of any malignancies in patients treated for multiple sclerosis. A Danish registry-based cohort	Magyari M, Foch C, Nørgaard M, Boutmy E, Veres K, Sabidó M	A-1026-0034-01799	Scientific Session 2: Safety assessment in the post-approval phase - real world evidence Session Date: 11.09.2019 Presenting Time: 15:01-15:13 h.
Increase of naïve B cells M2 macrophages and reduction of memory B/T cells during immune repopulation at 96 weeks in CLARITY assessed by Immune cell deconvolution	Giovannoni G, Leist T, Soelberg-Sorensen P, Kalatskaya I, Boschert U, DeMartino J, Rolfe A	A-1026-0031-00511	Session Title: Poster Session 2 Session Date: 12.09.2019 Presenting Time: 17:15-19:15 h.
Long-term effectiveness in patients previously enrolled in the Cladribine Tablets pivotal trials: a Real-World Evidence analysis using data from the Italian Multiple Sclerosis	Patti F, Visconti A, Capacchione A, Trojano M on behalf of the CLARINET-MS study group	A-1026-0031-00516	Session Title: Poster Session 1 Session Date: 11.09.2019 Presenting Time: 17:15-19:15 h.

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Registry (CLARINET-MS)			
Comparative effectiveness of Cladribine tablets vs other drugs in relapsing-remitting multiple sclerosis: an approach merging randomized controlled trial with real life data	Signori A, Saccà F, Lanzillo R, Maniscalco GT, Signoriello E, Repice A, Annovazzi P, Baroncini D, Clerico M, Binello E, Cerqua R, Mataluni G, Perini P, Bonavita S, Lavorgna L, Zarbo IR, Laroni A, Gutierrez LP, Gioia SL, Frigeni B, Barcella V, Frau J, Cocco E, Fenu G, Clerici VT, Sartori A, Rasia S, Cordioli C, Stromillo ML, Di Sapio A, Pontecorvo S, Grasso R, Barone S, Barrilà C, Russo CV, Esposito S, Ippolito D, Landi D, Visconti A, Sormani MP	A-1026-0031-00187	Session Title: Poster Session 2 Session Date: 12.09.2019 Presenting Time: 17:15-19:15 h
CD4+ T cells and CD19+ B cells respond differentially to cladribine treatment in vitro depending on their activation status. Role of deoxycytidine kinase	Carlini F, Ivaldi F, Boschert U, Visconti A, de Rosbo NK, Uccelli A	P1353	Session Title: Poster Session 3 Session Date: 13.09.2019 Presenting Time: 12:15-14:15 h.
Studying the effect of cladribine on microglia survival, proliferation, activation and cytokine release	Eixarch H, Calvo-Barreiro L, Fissolo N, Boschert U, Comabella M, Montalban X, Espejo C	P610	Session Title: Poster Session 1 Session Date: 11.09.2019 Presenting Time: 17:15-19:15 h.
Effects of 2-chlorodeoxyadenosine (Cladribine) on Microglial cells and Astrocytes	Aybar F, Perez MJ, Pasquini JM, Correale J	P623	Session Title: Poster Session 1 Session Date: 11.09.2019 Presenting Time: 17:15-19:15 h.

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Understanding the mechanisms of action of Cladribine in innate immune cells in MS	C. Rodríguez-Mogeda, S. Van der Pol, A.J. Van het Hof, HE. De Vries	P984	Session Title: Poster Session 2 Session Date: 12.09.2019 Presenting Time: 17:15-19:15 h
Year 1 Performance of adveva®, a Patient Support Programme for patients taking MAVENCLAD (cladribine tablets) in UK	Lyons M, Lott N, Morgan K	A-1026-0037-01914	ePoster
Cladribine is not mutagenic to mitochondrial DNA and RNA in leukemic cell lines	Järvinen E, Tienari PJ, Battersby BJ	P698	Session Title: Poster Session 1 Session Date: 11.09.2019 Presenting Time: 17:15-19:15 h.
Cladribine modify functional properties of murine microglia	Jørgensen LØ, Hyrlov KH, Elkjær ML, Pedersen AE, Svenningsen ÅF, Illes Z	A-1026-0031-01729	Session Title: Poster Session 2 Session Date: 12.09.2019 Presenting Time: 17:15-19:15 h
Safety data from the non-interventional, prospective study CLEVER (CLadribine Tablets – EValuation of thERapy satisfaction) and CLADQoL (CLADribine Tablets – evaluation of Quality of Life)	Penner, I-K, Ziemssen T, Nolting A, Hübschen M, Richter J, Schel E, Wagner T, Mueller B, Posevitz-Fejfar A	A-1026-0031-01026	Session Title: Poster Session 1 Session Date: 11.09.2019 Presenting Time: 17:15-19:15 h.
Non-interventional, prospective study CLEVER (CLadribine Tablets – EValuation of thERapy satisfaction)	Ziemssen T, Grothe C, Reifschneider G, Morgenbesser T, Richter J, Schel E, Wagner T, Müller B, Posevitz-Fejfar A	A-1026-0031-01164	Session Title: Poster Session 1 Session Date: 11.09.2019 Presenting Time: 17:15-19:15 h.
Non-interventional, prospective study CLADQoL (CLADribine Tablets - evaluation of Quality of Life)	Penner, I-K, Raji A, Pul R, Kallmann BA, Richter J, Schel E, Wagner T, Müller B, Posevitz-Fejfar A	A-1026-0031-01120	ePoster

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Cladribine tablets versus other disease-modifying oral treatments in multiple sclerosis (MS) in achieving no evidence of radiological and clinical disease activity (NEDA) - network meta-analysis (NMA)	Bartosik-Psujek H, Kaczyński Ł, Górecka M, Rolka M, Wójcik R, Kaczor M P, Zięba P	A-1026-0037-01912	Session Title: Poster Session 2 Session Date: 12.09.2019 Presenting Time: 17:15-19:15 h.
Cladribine tablets: Observational evaluation of effectiveness, safety, and patient reported outcomes in suboptimally controlled patients previously taking injectable disease-modifying drugs for relapsing forms of multiple sclerosis (CLICK-MS)	Miravalle A A, Katz J, Sloane J, Hayward B, Walsh J S, Harlow D E	A-1026-0033-01906	ePoster
Risk reduction of EDSS progression in patients with relapsing multiple sclerosis treated with cladribine tablets in the CLARITY study: post-hoc analysis including patients who went on to receive rescue therapy	Thrower B, Fox E J, Damian D, Lebson L, Dangond F	A-1026-0031-01938	Session Title: Poster Session 1 Session Date: 11.09.2019 Presenting Time: 17:15-19:15 h.
In depth analysis of B cells in multiple sclerosis patients after treatment with cladribine	Marsh-Wakefield F, Juillard P, Ashhurst T, McGuire H, Byrne SN, Hawke S, Grau GE	P1225	Session Title: Poster Session 3 Session Date: 13.09.2019 Presenting Time: 12:15-14:15 h.
FIMS Study: Exploration of Factors which Influence treatment decisions of patients with Multiple Sclerosis	Bardsley B, Cinc E, Heriot E, Lazarus K-J, McMurtrie M, Haynes J, Coleman E, Macdonell R	P676	Session Title: Poster Session 1 Session Date: 11.09.2019 Presenting Time: 17:15-19:15 h.
Markers of premature immunosenescence in the peripheral blood of multiple sclerosis subjects vs. healthy controls	Clénet ML, Daigneault A, Laurent C, Jamann H, Mamane V, Ouedraogo O, Carmena Moratalla A,	A-1026-0029-01320	Session Title: Poster Session 1 Session Date: 11.09.2019

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	Duquette P, Rousseau MC, Arbour N and Larochelle C		Presenting Time: 17:15-19:15 h.
MAVENCLAD® (cladribine) tablets Late-Breaker Presentation			
Cladribine decreases CD95 expressing CD4+ and CD8+ cells in lymphoid organs in naïve marmosets (Callithrix jacchus)	Kap Y, Boschert U, t'Hart B	A-1026-0000-02694	Session Title: Poster Session 3 Session Date: 13.09.2019 Presenting Time: 12:15-14:15
Rebif® (interferon beta-1a) Presentations			
Effect of Interferon β-1a Treatment on Serum Neurofilament Light Chain Levels in Patients with a First Clinical Demyelinating Event in the REFLEX trial	Kuhle J, Leppert D, Comi G, De Stefano N, Kappos L, Freedman MS, Roy S, Issard D	A-1026-0035-00622	Session Title: Poster Session 3 Session Date: 13.09.2019 Presenting Time: 12:15-14:15 h.
Pharmacodynamic biomarkers of interferon β-1a: Assessment in patients receiving long-term treatment with subcutaneous interferon β-1a in REFLEX and REFLEXION	Freedman MS, Wojcik J, D'Antonio M, Hyvert Y, Stinchi S, D'Urso V, Dangond F	A-1026-0033-00634	Session Title: Poster Session 3 Session Date: 13.09.2019 Presenting Time: 12:15-14:15 h.
Efficacy of subcutaneous interferon β-1a in patients with a first clinical demyelinating event: the REbif FLEXible dosing in early multiple sclerosis (REFLEX) study – outcomes in patients stratified by the 2017 McDonald criteria	Freedman MS, Kappos L, Comi G, De Stefano N, Roy S, Issard D	A-1026-0031-00626	Session Title: Poster Session 3 Session Date: 13.09.2019 Presenting Time: 12:15-14:15 h.
Post-hoc Analysis to Evaluate the Effects of Subcutaneous Interferon β-1a in Subgroups of Patients from the PRISMS Study with Early Onset vs Late Onset Disease	Freedman MS, Brod S, Wray S, Singer B, Dangond F, Issard D, Harlow D, Jack D	A-1026-0031-00628	ePoster

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Assessing the duration of EDSS improvement after a therapy start: a new statistical approach applied to the long term extension of the PRISMS study	Signori A, Bovis F, Carmisciano L, Alexandri N, Sormani M P	A-1026-0035-00443	Session Title: Poster Session 3 Session Date: 13.09.2019 Presenting Time: 12:15-14:15 h.
Effectiveness of subcutaneous interferon beta-1a 22/44 µg versus teriflunomide in newly treated patients with multiple sclerosis. A study in a French nationwide cohort of Multiple Sclerosis: Observatoire Francais de la sclérose en plaques (OFSEP)	Rollot F, Foch C, Laplaud D, Boutmy E, Marhardt K, Sabido S	A-1026-0034-00636	Session Title: Poster Session 2 Session Date: 12.09.2019 Presenting Time: 17:15-19:15 h.
Prevalence of infant outcomes at birth after exposure to interferon beta prior to or during pregnancy: A register-based cohort study in Finland and Sweden among women with MS	Vattulainen P, Burkill S, Geissbuehler Y, Sabidó M, Popescu C, Adamo A, Myhr K-M, Montgomery S, Korhonen P, the European Interferon Beta Pregnancy Study Group and the Nordic MS Pregnancy & Interferon Beta study group	A-1026-0009-01725	Session Title: Poster Session 3 Session Date: 13.09.2019 Presenting Time: 12:15-14:15 h.
Systematic mapping of the global educational offerings for multiple sclerosis patients on the topic of disease progression	Bharadia T, Kesselring J, Boyko A, Sumelahti M-L on behalf of the MS in the 21st Century initiative, and Alexandri N	A-1026-0005-01837	Session Title: Poster Session 2 Session Date: 12.09.2019 Presenting Time: 17:15-19:15 h.
Family planning decisions in people with multiple sclerosis	Lavorgna L, Worton H, S Russell, Jack D	A-1026-0009-00639	Session Title: Poster Session 3 Session Date: 13.09.2019 Presenting Time: 12:15-14:15 h.
Evobrutinib (Bruton's Tyrosine Kinase Inhibitor) Presentations			
Bruton's tyrosine kinase (BTK) inhibition promotes myelin repair in two different models of demyelination	Aigrot M S, Martin E, Grenningloh R, Stankoff B, Lubetzki C, Boschert U, Zalc B	A-1026-0025-01553	Session Title: Poster Session 3 Session Date: 13.09.2019 Presenting Time: 12:15-14:15 h.

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Inhibition of Bruton's Tyrosine Kinase Selectively Prevents Antigen-Activation of B cells and Ameliorates B cell-Mediated Experimental Autoimmune Encephalomyelitis	Torke S, Häusler D, Grenningloh R, Boschert U, Brück W and Weber M S	A-1026-0031-01785	Session Title: Poster Session 2 Session Date: 12.09.2019 Presenting Time: 17:15-19:15 h.
Effect of evobrutinib, a Bruton's tyrosine kinase inhibitor, on immune cell and immunoglobulin levels over 48 weeks in a phase 2 study in relapsing multiple sclerosis	Montalban X, Shaw J, Syed S, Dangond F, Martin E C, Grenningloh R, Weber MS, on behalf of the Evobrutinib Phase 2 Study Group	A-1026-0031-01645	Session Title: Poster Session 3 Session Date: 13.09.2019 Presenting Time: 12:15-14:15 h.

About MAVENCLAD®
MAVENCLAD, approved by the U.S. Food and Drug Administration (FDA) on March 29, 2019, is the first and only short-course oral therapy for the treatment of adults with relapsing-remitting disease (RRMS) and active secondary progressive disease (SPMS). Because of its safety profile, use of MAVENCLAD is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of multiple sclerosis (MS), and MAVENCLAD is not recommended for use in patients with clinically isolated syndrome (CIS). Patients should follow healthcare provider instructions including cancer screening, contraception and blood tests. The approved dose of MAVENCLAD is 3.5 mg per kg body weight over two years, administered as one treatment course of 1.75 mg per kg per year, each consisting of two treatment weeks. The mechanism by which cladribine exerts its therapeutic effects in patients with multiple sclerosis has not been fully elucidated but is thought to involve cytotoxic effects on B and T lymphocytes through impairment of DNA synthesis, resulting in depletion of lymphocytes. MAVENCLAD causes a dose-dependent reduction in lymphocyte counts followed by recovery.

Because cladribine is cytotoxic, special handling and disposal instructions should be followed.

MAVENCLAD has been approved in over 60 countries, including the European Union (EU), Canada, Australia and Switzerland, for various relapsing MS indications. Visit www.MAVENCLAD.com for more information.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: MALIGNANCIES and RISK OF TERATOGENICITY

- **Treatment with MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy; evaluate the benefits and risks of the use of MAVENCLAD on an individual patient basis for patients with prior or increased risk of malignancy.**
- **MAVENCLAD is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception because of the potential for fetal harm.**

CONTRAINDICATIONS

- Current malignancy.
- Pregnancy, and women and men of reproductive potential who do not plan to use effective contraception during MAVENCLAD dosing and for 6 m after the last dose in each treatment course.

- Human immunodeficiency virus (HIV).
- Active chronic infections (e.g., hepatitis or tuberculosis).
- History of hypersensitivity to cladribine.
- Breastfeeding while taking MAVENCLAD and for 10 days after the last dose.

DOSING CONSIDERATIONS: After the completion of 2 treatment courses, do not administer additional MAVENCLAD during the next 2 years. The risk of malignancy with reinitiating MAVENCLAD more than 2 years after completion of 2 treatment courses has not been studied.

ADDITIONAL WARNINGS AND PRECAUTIONS

- **Lymphopenia:** In clinical studies, 87% of MAVENCLAD-treated patients experienced lymphopenia. Concomitant use of MAVENCLAD with hematotoxic drugs may increase the risk of adverse reactions because of the additive hematological effects. Monitor lymphocyte counts before and during treatment, periodically thereafter, and when clinically indicated.
- **Infections:** Infections occurred in 49% of MAVENCLAD-treated patients compared to 44% of patients treated with placebo in clinical studies. The most frequent serious infections included herpes zoster and pyelonephritis. Single fatal cases of tuberculosis and fulminant hepatitis B were reported in the clinical program. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD. Screen patients for latent infections; consider delaying treatment until infection is fully controlled. Vaccinate patients antibody-negative to varicella zoster virus prior to treatment. Monitor for infections.
- **Hematologic Toxicity**: Mild to moderate decreases in neutrophil counts, hemoglobin levels, and platelet counts were observed. Severe decreases in neutrophil counts were observed in 3.6% of MAVENCLAD-treated patients, compared to 2.8% of placebo patients. Obtain complete blood count (CBC) with differential including lymphocyte count before and during treatment, periodically thereafter, and when clinically indicated.
- **Risk of Graft-versus-Host Disease With Blood Transfusions**: Irradiation of cellular blood components is recommended.
- **Liver Injury**: Obtain liver function tests prior to treatment. Discontinue MAVENCLAD if significant injury is suspected.
- **Hypersensitivity**: In clinical studies, 11% of MAVENCLAD-treated patients had hypersensitivity reactions, compared to 7% of placebo patients. Serious hypersensitivity reactions occurred in 0.5% of MAVENCLAD-treated patients, compared to 0.1% of placebo patients. If a hypersensitivity reaction is suspected, discontinue treatment. Do not use MAVENCLAD in patients with a history of hypersensitivity to cladribine.

Adverse Reactions: The most common adverse reactions with an incidence of >20% for MAVENCLAD are upper respiratory tract infection, headache, and lymphopenia.

Drug Interactions/Concomitant Medication: Concomitant use of MAVENCLAD with immunosuppressive or myelosuppressive drugs and some immunomodulatory drugs (e.g., interferon beta) is not recommended and may increase the risk of adverse reactions. Avoid concomitant use of certain antiviral and antiretroviral drugs. Avoid concomitant use of BCRP or ENT/CNT inhibitors as they may alter bioavailability of MAVENCLAD.

Please see the full **Prescribing Information,** including **boxed WARNING** for additional information.

About Rebif® (interferon beta-1a)
Rebif (interferon beta-1a) 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. It is used to decrease the frequency of relapses and delay the occurrence of some of the physical disability that is common in people with MS. The efficacy and safety of Rebif in controlled clinical trials beyond 2-years has not been established.

IMPORTANT SAFETY INFORMATION:
Rebif is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta, human albumin, or any other component of the formulation.

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Rebif should be used with caution in patients with depression, a condition that is common in people with multiple sclerosis. Depression, suicidal ideation, and suicide attempts have been reported to occur with increased frequency in patients receiving interferon compounds, including Rebif.

Severe liver injury, including some cases of hepatic failure requiring liver transplantation, has been reported rarely in patients taking Rebif. The potential for liver injury should be considered when used in combination with other products associated with liver injury. Monitor liver function tests and patients for signs and symptoms of hepatic injury. Consider discontinuing Rebif if hepatic injury occurs.

Anaphylaxis and other allergic reactions (some severe) have been reported as a rare complication of Rebif. Discontinue Rebif if anaphylaxis occurs.

In controlled clinical trials, injection site reactions occurred more frequently in Rebif-treated patients than in placebo-treated and Avonex-treated patients. Injection site reactions including injection site pain, erythema, edema, cellulitis, abscess, and necrosis have been reported in the postmarketing setting. Do not administer Rebif into affected area until fully healed; if multiple lesions occur, discontinue Rebif until skin lesions are healed.

Decreased peripheral blood counts in all cell lines, including pancytopenia, have been reported in Rebif-treated patients. In controlled clinical trials, leukopenia occurred at a higher frequency in Rebif-treated patients than in placebo and Avonex-treated patients. Thrombocytopenia and anemia occurred more frequently in 44 mcg Rebif-treated patients than in placebo-treated patients. Patients should be monitored for symptoms or signs of decreased blood counts. Monitoring of complete blood and differential white blood cell counts is also recommended.

Cases of thrombotic microangiopathy (TMA), some fatal, have been reported with interferon beta products, including Rebif, up to several weeks or years after starting therapy. Discontinue Rebif if clinical symptoms and laboratory findings consistent with TMA occur, and manage as clinically indicated.

Caution should be exercised when administering Rebif to patients with pre-existing seizure disorders. Seizures have been temporally associated with the use of beta interferons, including Rebif, in clinical trials and in postmarketing reports.

The most common side effects with Rebif are injection-site disorders, headaches, influenza-like symptoms, abdominal pain, depression, elevated liver enzymes, and hematologic abnormalities.

There are no adequate and well-controlled studies in pregnant women. Rebif should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Please see the full Prescribing Information for additional information:
http://www.emdserono.com/ms.country.us/en/images/Rebif_PI_tcm115_140051.pdf?Version=

About Evobrutinib
Evobrutinib (M2951) is in clinical development to investigate its potential as a treatment for multiple sclerosis (MS), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). It is an oral, highly selective inhibitor of Bruton's tyrosine kinase (BTK) which is important in the development and functioning of various immune cells including B lymphocytes and macrophages. Evobrutinib is designed to inhibit primary B cell responses such as proliferation and antibody and cytokine release, without directly affecting T cells. BTK inhibition is thought to suppress autoantibody-producing cells, which preclinical research suggests may be therapeutically useful in certain autoimmune diseases. Evobrutinib is currently under clinical investigation and not approved for any use anywhere in the world.

About Multiple Sclerosis
Multiple sclerosis (MS) is a chronic, inflammatory condition of the central nervous system and is the most common, non-traumatic, disabling neurological disease in young adults. It is estimated that approximately 2.3 million people have MS worldwide. While symptoms can vary, the most common symptoms of MS include blurred vision, numbness or tingling in the limbs and problems with strength and coordination. The relapsing forms of MS are the most common.

Merck KGaA, Darmstadt, Germany in Neurology and Immunology
Merck KGaA, Darmstadt, Germany, has a long-standing legacy in neurology and immunology, with significant R&D and commercial experience in multiple sclerosis (MS). The company`s current MS portfolio includes two products for the treatment of relapsing MS, with a robust pipeline focusing on discovering new therapies that have the potential to modulate key pathogenic mechanisms in MS. Merck

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KGaA, Darmstadt, Germany, aims to improve the lives of those living with MS, by addressing areas of unmet medical needs.

The company`s robust immunology pipeline focuses on discovering new therapies that have the potential to modulate key pathogenic mechanisms in chronic diseases such as MS, systemic lupus erythematosus (SLE) and forms of arthritis, including rheumatoid arthritis (RA) and osteoarthritis (OA).

All Merck KGaA, Darmstadt, Germany, press releases are distributed by e-mail at the same time they become available on the EMD Group Website. In case you are a resident of the USA or Canada please go to www.emdgroup.com/subscribe to register for your online subscription of this service as our geo-targeting requires new links in the email. You may later change your selection or discontinue this service.

About Merck KGaA, Darmstadt, Germany
Merck KGaA, Darmstadt, Germany, is a leading science and technology company in healthcare, life science and performance materials. Around 52,000 employees work to further develop technologies that improve and enhance life – from biopharmaceutical therapies to treat cancer or multiple sclerosis, cutting-edge systems for scientific research and production, to liquid crystals for smartphones and LCD televisions. In 2018, Merck KGaA, Darmstadt, Germany, generated sales of € 14.8 billion in 66 countries.

Scientific exploration and responsible entrepreneurship have been key to the company's technological and scientific advances. This is how Merck KGaA, Darmstadt, Germany, has thrived since its founding in 1668. The founding family remains the majority owner of the publicly listed company. Merck KGaA, Darmstadt, Germany, holds the global rights to the Merck name and brand. The only exceptions are the United States and Canada, where the business sectors of Merck operate as EMD Serono in healthcare, MilliporeSigma in life science, and EMD Performance Materials.