News Release

Your Contact
alice.mcgrail@emdserono.com
Phone: 1-781-681-2886

Not intended for UK-based media

October 26, 2022

Merck KGaA, Darmstadt, Germany Showcases Depth of MS Portfolio at ECTRIMS Supporting Commitment to Advancing MS Care

- **Company's scientific leadership will be highlighted in 39 abstracts presented across its multiple sclerosis (MS) portfolio**
- **Data on investigational BTK inhibitor evobrutinib demonstrate long-term disease stability in people living with relapsing MS (RMS)**
- **Phase IV study highlights improvement in measures of Quality of Life in people living with RMS after two years of treatment with MAVENCLAD® (cladribine) tablets**

Darmstadt, Germany, October 26, 2022 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced it will present 39 abstracts at the 38th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), being held October 26-28, 2022 in Amsterdam, the Netherlands. The breadth of data highlights the Company's scientific leadership in multiple sclerosis (MS) and includes a presentation on a clinical trial with long-term data on Expanded Disability Status Scale (EDSS) scores in people with relapsing MS (RMS) treated with evobrutinib, an investigational agent, as well as new data demonstrating MAVENCLAD® (cladribine) tablets improved Quality of Life (QoL) in people with highly active RMS over two years. Additionally, a two-year follow-up study showed the onset of action on the reduction of MRI lesions with MAVENCLAD being maintained from Month 2 through two years.

Frankfurter Strasse 250
64293 Darmstadt · Germany
Hotline +49 6151 72-5000
www.emdgroup.com

Head of Corporate Media Relations: +49 151 1454 2702
Spokespersons: +49 6151 72 -9591 / -45946 / -55707

News Release

"Multiple sclerosis has a profound impact on quality of life and improving this through therapy is often the most important outcome for people living with MS," said Gavin Giovannoni, Professor of Neurology, Queen Mary University of London. "The data presented at ECTRIMS further substantiate the therapeutic benefit of MAVENCLAD by improving Quality of Life measures over two years, combined with new evidence that the early effect on MRI lesions is maintained over that period."

In the final analysis of the open-label, single-arm, multicenter, Phase IV CLARIFY-MS study, statistically significant ($p \leq 0.0001$) improvements from baseline were observed for Multiple Sclerosis Quality of Life-54 (MSQoL-54) physical and mental health composite scores (mean changes of 4.86 and 4.80, respectively; $p<0.0001$). Changes in MSQoL-54 composite scores were consistent across treatment naïve and prior disease-modifying treatment (DMT) subgroups. Annualized relapse rate was 0.13 in all patients (0.08 in patients who had not received DMT prior to receiving MAVENCLAD) and median EDSS was unchanged over two years. No new safety concerns emerged.

Also to be presented are new MRI outcomes data from the Phase IV MAGNIFY-MS study, which demonstrated an onset of action from Month 2 with sustained reduction in MRI lesion counts maintained out to two years in people with highly active RMS treated with MAVENCLAD. The proportion of lesion-free patients increased from 47% at baseline to 86.2% at the end of the study (Month 18–24). In the study, MRI lesions at baseline were compared over multiple time periods, from initial screening to Month 24. Over the two years, the benefit:risk profile of MAVENCLAD remained unchanged and in line with observations made during the clinical trial program.

Additionally, updated post-approval safety data will be presented based on an analysis of 56,300 patients who received MAVENCLAD post-approval, representing 95,664 patient-years of experience, as of July 2022. The study found the safety profile of MAVENCLAD is consistent with findings from the clinical development program and the CLARIFY-MS and MAGNIFY-MS studies.

"The breadth of our data at ECTRIMS exemplifies our commitment to pushing forward scientific innovation with the development of evobrutinib, while generating new, meaningful data to demonstrate the safety profile and effectiveness of MAVENCLAD," said Jan Klatt, Senior Vice President, Head of Development Unit

News Release

Neurology & Immunology, Merck KGaA, Darmstadt, Germany. "Our goal is to ensure people living with MS, and those who treat them, have the information they need to manage their MS today and in the future."

Beyond the MAVENCLAD and evobrutinib data presented, Merck KGaA, Darmstadt, Germany will have several Company events, along with additional data from its MS portfolio at ECTRIMS 2022.

Company activities at ECTRIMS 2022:

- "Connecting the dots: immune cells and CNS inflammation" co-chaired by Professor Gavin Giovannoni, MBBCh, PhD, FCP (Neurol., SA), FRCP, FRCPath, Blizard Institute, Barts and the London School of Medicine and Dentistry, UK, and Celia Oreja-Guevara, MD, PhD, Hospital Clínico San Carlos, Madrid, Spain (October 26, 2022, 13:15-14:15 CEST)
- "New tools for new challenges in multiple sclerosis" chaired by Stephen Krieger, MD, Mount Sinai Hospital, New York, NY, USA (October 28, 2022, 14:15-15:15 CEST)
- Product Theater: Early Experience with MAVENCLAD by Ravi Dukkipati, MD, WellSpan Neurology, York, PA, USA

Below is the full list of Merck KGaA, Darmstadt, Germany-related abstracts accepted for presentation at ECTRIMS 2022:

Abstract Name	Authors	ID	Presentation Details
MAVENCLAD Poster Presentations			
Improvements in Quality of Life Over 2 Years in Patients Treated With Cladribine Tablets for Highly Active Relapsing Multiple Sclerosis: Final Analysis of CLARIFY-MS	Solari A, Montalban X, Lechner-Scott J, Piehl F, Brochet B, Langdon D, Hupperts R, Selmaj K, Havrdova EK, Patti F, Brieva L, Maida EM, Alexandri N, Smyk A, Nolting A, Keller B, on behalf of the CLARIFY Investigators	P108	**Session:** 1 **Date:** October 26, 2022 **Time:** 16:30- 18:30 CEST **Presenter:** Jeannette Lechner-Scott
Early Onset of Action and Sustained Efficacy of MRI Outcomes during Cladribine Tablets Treatment in Highly Active Relapsing Multiple	De Stefano N, Achiron A, Barkhof F, Chan A, Derfuss T, Hodgkinson S, Leocani L, Montalban X, Prat A, Schmierer K,	P717	**Session:** 2 **Date:** October 27, 2022 **Time:** 17:00- 19:00 CEST

News Release

Sclerosis: Results of the 2-year MAGNIFY-MS Study	Sellebjerg F, Vermersch P, Wiendl H, Keller B, Smyk A, Gardner L		**Presenter:** Nicola De Stefano
Updated Post-Approval Safety of Cladribine Tablets in the Treatment of Multiple Sclerosis, With Particular Reference to Liver Safety	Giovannoni G, Leist T, Jack D, Galazka A, Nolting A	P341	**Session:** 1 **Date:** October 26, 2022 **Time:** 16:30- 18:30 CEST **Presenter:** Gavin Giovannoni
High Adherence and Minimal Delays of Year 2 Treatment in People with Multiple Sclerosis Treated with Cladribine Tablets: Results from Multi-Country Patient Support Programmes	Oh J, Ayer M, Alroughani R, Lemieux C, Morgan K, D'Eramo M, Vella T, Boshra A, de Souza S, Verdun di Cantogno E, Sabidó M	P727	**Session:** 2 **Date:** October 27, 2022 **Time:** 17:00 CEST **Presenter:** Jiwon Oh
Treatment Emergent Adverse Events Experienced Early and Transiently in the Treatment Course with Cladribine Tablets: Data from the CLEVER Real-World Study	Ziemssen T, Posevitz-Fejfar, Wagner T, Übler S, Richter J, Müller B, Penner I-K	P772	**Session:** 2 **Date:** October 27, 2022 **Time:** 17:00- 19:00 CEST **Presenter:** Talf Ziemssen
Maven4: Phase IV Non-Interventional, Prospective, Spanish Multicenter Study to Evaluate Cladribine Tablets Long Term Effectiveness on Real-World Clinical Practice	Saiz A, Aladro Benito Y, Costa-Frossard F, Sánchez Magro I, Rodríguez Antigüedad A	P774	**Session:** 2 **Date:** October 27, 2022 **Time:** 17:00- 19:00 CEST **Presenter:** Albert Saiz
Cladribine Protects SH-SY5Y Neuron-Like Cells from Oxidative Stress Conditions In Vitro	Eixarch H, Calvo-Barreiro L, Fissolo N, Boschert U, Comabella M, Montalban X, Espejo C	P784	**Session:** 2 **Date:** October 27, 2022 **Time:** 17:00- 19:00 CEST **Presenter:** Herena Eixarch
Real-World Use of Cladribine Tablets (Completion Rates and Treatment Persistence) in Patients With Multiple Sclerosis in England: The CLARENCE Study	Brownlee W, Amin A, Herbert A, Ashton L	P762	**Session:** 2 **Date:** October 27, 2022 **Time:** 17:00 CEST **Presenter:** Wallace Brownlee
Decision-making Factors in Patient Choice to Initiate Treatment with Cladribine: A Preliminary Baseline Analysis From the STATURE Study	Allan M, Grech L, Cartwright A, Harding J, Mardan J, O'Maley J, Savickas S, Sharma M,	P304	**Session:** 1 **Date:** October 26, 2022 **Time:** 16:30- 18:30 CEST

News Release

	Murambiwa P, Stockle P, Bardsley B, Butler E		**Presenter:** Michelle Allan
Assessment of Treatment Satisfaction Across Oral DMTs for Multiple Sclerosis: a Preliminary Baseline Analysis from the STATURE Study.	Grech L, Allan M, Cartwright A, Harding J, Mardan J, O'Maley T, Savickas S, Sharma M, Murambiwa P, Stockle P, Bardsley B, Butler E	EP1086	**Session:** ePoster **Date:** October 26-28, 2022
A Real-World Study of Four-Year Follow Up Study of Patients Treated with Oral Cladribine From 2018-2022	O'Neill DTD, Sharma M, Dong G, Hodgkinson SJ	EP1132	**Session:** ePoster **Date:** October 26-28, 2022
A Study of Activated and Naïve T Regs and B Cell Subsets For 30 Months After the Use of Cladribine	Hodgkinson SJ, O'Neill DTD, Sharma M, Dong G, Verma ND, Al-atiyah R, Hall BM	P704	**Session:** 2 **Date:** October 27, 2022 **Time:** 17:00- 19:00 CEST **Presenter:** Suzanna Hodgkinson
CLADCOMS - CLADribine Tablets Long-Term Control of MS – a Post-Marketing Investigator Driven Study	Fink K, Nilsson P, Alonso L, Sveningsson A, Gunnarsson M, Lange N, Ayad A, Vrethem M, Burman J, Lycke J, Piehl F	EP1060	**Session:** ePoster **Date:** October 26-28, 2022
Clinical Effectiveness and Safety of Cladribine Tablets for Patients Treated at least 12 Months in the Swedish Post-Market Surveillance Study "Immunomodulation and Multiple Sclerosis Epidemiology 10" (IMSE 10)	Rosengren V, Ekström E, Forsberg L, Hillert J, Nilsson P, Dahle C, Svenningsson A, Lycke J, Landtblom A-M, Burman J, Martin C, Sundström, Gunnarsson M, Piehl F, Olsson T	P728	**Session:** 2 **Date:** October 27, 2022 **Time:** 17:00- 19:00 CEST **Presenter:** Linda Forsberg
SARS-CoV2 Exposure Rates and Serological Response of People Living With MS	Longinetti E, Asplund K, Kockum I, Englund S, Burman J, Fink K, Fogdell-Hahn A, Gunnarsson M, Hillert J, Langer-Gould A, Lycke J, Nilsson P, Salzer J, Svenningsson A, Mellergård J, Frisell T, Olsson T, Piehl F	P558	**Session:** 2 **Date:** October 27, 2022 **Time:** 17:00- 19:00 CEST **Presenter:** Elisa Longinetti
COVID-19 Humoral and T-cell Mediated Vaccination	Vickaryous N, Rios F, Schalk L, Asardag AN, George K, Kang A, Baker	P781	**Session:** 2 **Date:** October 27, 2022

News Release

Responses in People with Multiple Sclerosis	D, Giovannoni G, Dobson R		**Time:** 17:00- 19:00 CEST **Presenter:** Nikki Vickaryous
Differences Between Clinical Trials and "Real-World" Use of Disease Modifying Therapies: Insights from the UK OPTIMISE:MS Pharmacovigilance Study	Dobson R, Matthews P, Miller A, Pindoria J, Waddingham E	P763	**Session:** 2 **Date:** October 27, 2022 **Time:** 17:00- 19:00 CEST **Presenter:** Ruth Dobson
Cladribine Treatment Exerts Specific Effects on Memory B Cell Immunoglobulin Repertoires in Multiple Sclerosis Patients	Ruschil C, Gabernet G, Kemmerer CL, Ziemann U, Nahnsen S, Kowarik MC	EP1115	**Session:** ePoster **Date:** October 26-28, 2022 **Presenter:** Christoph Ruschil
Cladribine Effects on T and B Cell Subsets and T Cell Reactivity in Multiple Sclerosis	Hansen RH, von Essen MR, Mahler MR, Cobanovic S, Binko TS, Sellebjerg F	P697	**Session:** 2 **Date:** October 27, 2022 **Time:** 17:00- 19:00 CEST **Presenter:** Rikke Holm Hansen
Safety and Efficacy of Cladribine Therapy Following a Treatment with Anti-CD20 Compounds in Relapsing Multiple Sclerosis Patients: A Pilot Study	Sacco R, Disanto G, Pravatà E, Gobbi C, Zecca C	EP1068	**Session:** ePoster **Date:** October 26-28, 2022
Evobrutinib Poster Presentations			
Evobrutinib, a Bruton's Tyrosine Kinase Inhibitor, Maintains Lowered Serum Neurofilament Light Chain Levels Over 2.5 Years of Treatment, in Patients With Relapsing Multiple Sclerosis	Kuhle J, Kappos L, Montalban X, Benkert P, Li Y, Thangavelu K, Hyvert Y, Tomic D	EP1021	**Session:** ePoster **Date:** October 26-28, 2022 **Presenter:** Jens Kuhle
MRI and Clinical Outcomes of Evobrutinib, a Bruton's Tyrosine Kinase Inhibitor, in Relapsing Multiple Sclerosis Over 2.5 Years of the Open-label Extension to a Phase II Trial	Vermersch P, Arnold D, Wolinsky JS, Havrdova E, Kinkolykh A, Hyvert Y, Tomic D, Montalban X	P731	**Session:** 2 **Date:** October 27, 2022 **Time:** 17:00- 19:00 CEST **Presenter:** Patrick Vermersch
Evobrutinib Exert a Therapeutic Action on EAE by Increasing the Peripheral and	Serrano-Regal MP, Calahorra L, Alonso-García I, Grenningloh R,	P307	**Session:** 1 **Date:** October 26, 2022

News Release

Central Classical Dendritic Cell Number and Maturation	Boschert U, Haselmayer P, Ortega MC, Machín-Díaz I, Camacho-Toledano C, García-Arocha J, Clemente D		**Time:** 16:30- 18:30 CEST **Presenter:** Mari Paz Serrano-Regal
Evobrutinib, a Bruton's Tyrosine Kinase Inhibitor, Acts on Microglia: Implications in the Treatment of Progressive Mechanisms in Multiple Sclerosis	Geladaris A, Torke S, Grenningloh R, Boschert U, Brück W, Weber MS	P693	**Session:** 2 **Date:** October 27, 2022 **Time:** 17:00- 19:00 CEST **Presenter:** Anastasia Geladaris
B cells infiltrating the MS brain: from local maturation to targeting by evobrutinib	Bogers L, van Langelaar J, Rijvers L, Engelenburg HJ, Melief M-J, Wierenga-Wolf AF, Rip J, Blok KM, de Vries HE, Hendriks RW, Boschert U, Smolders J, van Luijn MM	P147	**Session:** 1 **Date:** October 26, 2022 **Time:** 16:30- 18:30 CEST **Presenter:** Laurens Bogers
Immune response following mRNA COVID-19 vaccination in patients with multiple sclerosis treated with the Bruton's tyrosine kinase inhibitor evobrutinib	Bar-Or A, Cross AH, Cunningham A, Hyvert Y, Seitzinger A, Drouin EE, Alexandri N, Tomic D, Montalban X	P1188	**Session:** 1 **Date:** October 26, 2022 **Time:** 16:30- 18:30 CEST **Presenter:** Amit Bar-Or
Rebif® (interferon beta-1a) Subcutaneous Injection Poster Presentations			
Exploring the Relationship Between Serum GDF-15 and Disease Stability in Patients with a First Clinical Demyelinating Event Treated with Subcutaneous Interferon β-1a or Placebo in the REFLEX Study	Coray M, Freedman MS, Barkhof F, Comi G, De Stefano N, Kappos L, Enz L, Seitzinger A, Jack D, Kuhle J, Mehling M	EP1027	**Session:** ePoster **Date:** October 26-28, 2022 **Presenter:** Mali Coray
Evolution of the RebiSmart® Autoinjector Device in Support of Adherence to Subcutaneous Interferon Beta-1a Therapy for Relapsing Multiple Sclerosis	Arnaud L, Keiser M, Henninger E, Piras F, Seitzinger A, Jack D, Le Masne Q	EP1079	**Session:** ePoster **Date:** October 26-28, 2022 **Presenter:** Dominic Jack
Validation of a Semi-Automated Method to Quantify Lesion Volume Changes in Multiple Sclerosis on 2D Proton Density-Weighted Images Using Subtraction Imaging	Mattiesing RM, Stel S, Mangroe AS, Brouwer I, Versteeg A, van Schijndel RA, Uitdehaag BMJ, Barkhof F, Vrenken H	P634	**Session:** 2 **Date:** October 27, 2022 **Time:** 17:00- 19:00 CEST **Presenter:** Rozemarijn M Mattiesing

News Release

Expression of peripheral blood IFN-inducible genes predicts treatment outcome in patients with secondary progressive multiple sclerosis treated with IFN-beta-1a	Gurevich M, Zilkha-Falb R, Menascu S, Magalashvili D, Dolev M, Sonis P, Mandel M, Achiron A	P353	**Session:** 1 **Date:** October 26, 2022 **Time:** 16:30- 18:30 CEST **Presenter:** Michael Gurevich
Non-Product Specific Poster Presentations			
DISCOntinuation of disease-modifying therapies in MS (DISCOMS) Extension – Study Design and Baseline Demographics to Date	Engebretson E, Cutter G, Fox R, Kister I, Miller A, Morgan C, Seale R, Corboy JR	EP1089	**Session:** ePoster **Date:** October 26-28, 2022
Expert Opinion on the Use of Contraception in People with Multiple Sclerosis	Hillert J, Bove R, Haddad L, Hellwig K, Houtchens M, Magyari M, Mercki G, Montgomery S, Nappi R, Stenager E, Thompson H, Tulek Z, Verdun di Cantogno E, Simoni M	P080	**Session:** 1 **Date:** October 26, 2022 **Time:** 16:30- 18:30 CEST **Presenter:** Jan Hillert
Single-Cell RNA Sequencing of Peripheral CD8+ T Cells of MS-Discordant Monozygotic Twins Reveals Disease-Associated Alterations In Immune Signaling	Kavaka V, Mutschler L, Eglseer K, Flierl-Hecht A, Kümpfel T, Hohlfeld R, Kerschensteiner M, Gerdes L.A, Beltran E	P159	**Session:** 1 **Date:** October 26, 2022 **Time:** 16:30- 18:30 CEST **Presenter:** Vladyslav Kavaka
Caregiver Burden and Associated Factors Among Caregivers of Persons with Multiple Sclerosis: Application of a Specific Instrument	Vanotti S, Roman MS, Ferrandina F, Bauer J, Rosa R, Casas Parera I, Saladino ML, Caceres F	EP0864	**Session:** ePoster **Date:** October 26-28, 2022 **Presenter:** Sandra Vannoti
Evolutionarily Conserved Signatures of Microglia in Health and Disease	Salinas V, Manouchehri N, Hussain R, Stuve O	P131	**Session:** 1 **Date:** October 26, 2022 **Time:** 16:30- 18:30 CEST **Presenter:** Victor Salinas
Peripheral Blood Immune Markers Associated With Immunosenescence in Multiple Sclerosis and Healthy Controls	Carpentier Solorio Y, Daigneault A, Tastet O, Clénet M-L, Farzam-kia N, Levert A, Da Cal S, Clément W, Jamann H, Laurent C, Mamane VH, Ouedraogo O, Moratalla AC, Balthazard R, Lahav B, Prat A, Girard J-M, Duquette P, Rousseau M-C, Arbour N, Larochelle C	P545	**Session:** 2 **Date:** October 27, 2022 **Time:** 17:00- 19:00 CEST **Presenter:** Catherine Larochelle

News Release

Chemerin Correlates with MS Progression Parameters and Affects Intracellular Metabolism in Human Microglia and Macrophages	Loonstra FC, van der Pol SM, Falize KF, van Heertum T, de Ruiter LR, Schoonheim MM, Killestein J, Uitdehaag BMJ, Kooij G, de Vries HE, Rijnsburger M	P551	**Session:** 2 **Date:** October 27, 2022 **Time:** 17:00- 19:00 CEST **Presenter:** Merel Rijnsburger
Amyloid and some tau Proteinopathy are Observed in a Subset of Individuals with Multiple Sclerosis	Taga M, Duquesne L, Lee A, Sigalov A, Peralta Cruz F, De Jager P	P1204	**Session:** 2 **Date:** October 27, 2022 **Time:** 17:00- 19:00 CEST
Non-Product Specific Oral Presentations			
Biological Roles of Myeloid Cell Subsets During CNS Inflammation	Manouchehri N, Victor, Hussain RZ, Stuve O	O124	**Session:** Young Scientific Investigators' Session 3: Long-term outcomes and safety **Date:** October 27, 2022 **Time:** 15:00- 16:00 CEST **Presenter:** Navid Manouchehri

About Evobrutinib

Evobrutinib is an oral, CNS-penetrating, highly selective inhibitor of Bruton's tyrosine kinase (BTK) in clinical development as a potential treatment for relapsing multiple sclerosis (RMS). It is the first BTK inhibitor to demonstrate clinical efficacy in the largest Phase II study with follow-up beyond three years as well as demonstrate an impact on early biomarkers of ongoing central inflammation that correlate with disease progression, including slowly expanding lesions (SEL) volume and levels of blood neurofilament light chain protein (NfL). Evobrutinib is designed to modulate B cell responses such as proliferation and antibody and cytokine release, as well as modulate macrophage/microglia activation. During Phase II, the BTKi dose finding study demonstrated that BID dosing achieved maximal efficacy with >95% BTK occupancy maintained in 98% of patients before the next dose. Evobrutinib is currently under clinical investigation and is not approved for any use anywhere in the world.

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 80 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

WARNING: MALIGNANCIES and RISK OF TERATOGENICITY

- **Treatment with MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy. In patients with prior malignancy or with increased risk of malignancy, evaluate the benefits and risks of the use of MAVENCLAD on an individual patient basis. Follow standard cancer screening guidelines in patients treated with MAVENCLAD**
- **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. Malformations and embryolethality occurred in animals. Exclude pregnancy before the start of treatment with MAVENCLAD in females of reproductive potential. Advise females and males of reproductive potential to use effective contraception during MAVENCLAD dosing and for 6 months after the last dose in each treatment course. Stop MAVENCLAD if the patient becomes pregnant**

CONTRAINDICATIONS

- Patients with current malignancy.
- Pregnant women, and women and men of reproductive potential who do not plan to use effective contraception during and for 6 months after the last dose in each treatment course. May cause fetal harm.
- Patients with human immunodeficiency virus (HIV).
- Patients with active chronic infections (e.g., hepatitis or tuberculosis).
- Patients with a history of hypersensitivity to cladribine.
- Women intending to breastfeed while taking MAVENCLAD tablets and for 10 days after the last dose.

WARNINGS AND PRECAUTIONS

- **Malignancies:** Treatment with MAVENCLAD may increase the risk of malignancy. After the completion of 2 treatment courses, do not administer additional MAVENCLAD treatment during the next 2 years. In clinical studies, patients who received additional MAVENCLAD treatment within 2 years after the first 2 treatment courses had an increased incidence of malignancy. The risk of malignancy with reinitiating MAVENCLAD more than 2 years after the completion of 2 treatment courses has not been studied. Follow standard cancer screening guidelines in patients treated with MAVENCLAD.

- **Risk of Teratogenicity:** MAVENCLAD may cause fetal harm when administered to pregnant women. In females of reproductive potential, exclude pregnancy before initiation of each treatment course of MAVENCLAD and prevent by the use of effective contraception during MAVENCLAD dosing and for at least 6 months after the last dose of each treatment course. Women who become pregnant during treatment with MAVENCLAD should discontinue treatment.
- **Lymphopenia:** MAVENCLAD causes a dose-dependent reduction in lymphocyte count. In clinical studies, 87% of MAVENCLAD-treated patients experienced lymphopenia. The lowest absolute lymphocyte counts occurred approximately 2 to 3 months after the start of each treatment course and were lower with each additional treatment course. 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:** MAVENCLAD can reduce the body's immune defense and may increase the likelihood of 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. Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter. Monitor for infections. In patients treated with parenteral cladribine for oncologic indications, cases of progressive multifocal leukoencephalopathy (PML) have been reported. No case of PML has been reported in clinical studies of cladribine in patients with MS.
- **Hematologic Toxicity:** In addition to lymphopenia, decreases in other blood cells and hematological parameters have been reported with MAVENCLAD in clinical studies. In general, 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:** Transfusion-associated graft-versus-host disease has been observed rarely after transfusion of nonirradiated blood in patients treated with cladribine for non-MS treatment indications.
- **Liver Injury:** In clinical studies, 0.3% of MAVENCLAD-treated patients had liver injury (serious or causing treatment discontinuation) compared to 0 placebo patients. Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to treatment. Discontinue if clinically significant injury is suspected.
- **Hypersensitivity:** In clinical studies, 11% of MAVENCLAD-treated patients had hypersensitivity reactions, compared to 7% of placebo patients. Hypersensitivity reactions that were serious and/or led to discontinuation of

MAVENCLAD, occurred in 0.5% of MAVENCLAD-treated patients, compared to 0.1% of placebo patients. If a hypersensitivity reaction is suspected, discontinue MAVENCLAD therapy. Do not use MAVENCLAD in patients with a history of hypersensitivity to cladribine.

- **Cardiac Failure:** In clinical studies, one MAVENCLAD-treated patient experienced life-threatening acute cardiac failure with myocarditis, which improved after approximately one week. Cases of cardiac failure have also been reported with parenteral cladribine used for treatment indications other than multiple sclerosis.

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. Acute short-term therapy with corticosteroids can be administered.

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.

Use in Specific Populations: Studies have not been performed in pediatric or elderly patients, pregnant or breastfeeding women. Use in patients with moderate to severe renal or hepatic impairment is not recommended.

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.

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.

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.

Epidemiological data do not suggest a clear relationship between interferon beta use and major congenital malformations, but interferon beta may cause fetal harm based on animal studies. Data from a large human population-based cohort study, as well as other published studies over several decades, have not identified a drug-associated risk of major birth defects with interferon beta products during early pregnancy. Findings regarding a potential risk for low birth weight or miscarriage with the use of interferon beta products in pregnancy have been inconsistent.

Please see the full Prescribing Information for additional information:
https://www.emdserono.com/us-en/pi/rebif-pi.pdf

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 2.8 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.

News Release

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 – Rebif® (interferon beta-1a) and MAVENCLAD® (cladribine) tablets. Merck KGaA, Darmstadt, Germany aims to improve the lives of patients by addressing areas of unmet medical needs. In addition to Merck KGaA, Darmstadt, Germany's commitment to MS, the company also has a pipeline focusing on discovering new therapies that have potential in other neuroinflammatory and immune-mediated diseases, including systemic lupus erythematosus (SLE), generalized myasthenia gravis (gMG) and neuromyelitis optica spectrum disorder (NMOSD).

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, change your selection or discontinue this service.

About Merck KGaA, Darmstadt, Germany
Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across life science, healthcare and electronics. Around 60,000 employees work to make a positive difference to millions of people's lives every day by creating more joyful and sustainable ways to live. From advancing gene editing technologies and discovering unique ways to treat the most challenging diseases to enabling the intelligence of devices – the company is everywhere. In 2021, Merck KGaA, Darmstadt, Germany, generated sales of € 19.7 billion in 66 countries.

The company holds the global rights to the name and trademark "Merck" internationally. The only exceptions are the United States and Canada, where the business sectors of Merck KGaA, Darmstadt, Germany, operate as MilliporeSigma in life science, EMD Serono in healthcare and EMD Electronics in electronics. Since its founding in 1668, scientific exploration and responsible entrepreneurship have been key to the company's technological and scientific advances. To this day, the founding family remains the majority owner of the publicly listed company.