News Release

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New MAVENCLAD® Data at ACTRIMS Forum 2022 Show Favorable Efficacy Outcomes Versus Other Oral DMTs and Lower Occurrence of Further Relapses or Disability Progression

- **New real-world data show MAVENCLAD® (cladribine) tablets had lower annualized relapse rates and longer time to first relapse and time to switch than fingolimod, dimethyl fumarate and teriflunomide in relapsing multiple sclerosis patients**
- **Additional clinical trial data show patients treated with MAVENCLAD early after a first clinical demyelinating event had a lower occurrence of further relapses or disability progression as compared to placebo**

Darmstadt, Germany, February 24, 2022 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced new real-world data from the MSBase Registry demonstrating MAVENCLAD® (cladribine) tablets had more favorable relapse outcomes and longer time to switch to another disease modifying therapy (DMT) compared to the oral DMTs fingolimod, dimethyl fumarate (DMF) and teriflunomide in relapsing multiple sclerosis (RMS) patients. A second study, analyzing real-world follow up of clinical trial patients with a first attack suggestive of MS, showed those treated with MAVENCLAD had a lower rate of conversion to clinically definite multiple sclerosis (CDMS), defined by further relapse or disability progression, and a lower risk of relapse than those not exposed to MAVENCLAD. These data will be presented at the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Forum 2022, taking place February 24-26, 2022.

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In this first analysis of its size from the Generating Learnings In MultiPle SclErosis (GLIMPSE) study, data from 633 patients prescribed MAVENCLAD in the MSBase Registry was matched using propensity scores to patients receiving fingolimod (n=1195), DMF (n=912) or teriflunomide (n=735). Results showed the annualized relapse rate (ARR) for patients treated with MAVENCLAD was 0.09 compared to 0.15, 0.15 and 0.17 for fingolimod, DMF and teriflunomide, respectively. Risk of first relapse in MAVENCLAD-treated patients was 40%, 42% and 67% lower than in patients treated with fingolimod, DMF and teriflunomide, respectively. The time to switch rate in patients treated with MAVENCLAD was 4, 7 and 6.5 times lower than fingolimod, DMF and teriflunomide, respectively. The GLIMPSE study was a longitudinal, retrospective analysis of adult patients identified with RMS from the MSBase Registry, an international online registry for neurologists studying MS and other neuro-immunological diseases.

"It is important in a lifelong disease like MS to continue assessing the efficacy and safety of available treatment options in the real world," said Helmut Butzkueven, MBBS, FRACP, PhD, Department of Neuroscience, Central Clinical School, Monash University, Melbourne. "This is where the MSBase Registry, using standardized data records from over 79,000 people with MS around the world, can provide information that is not possible to obtain in a randomized clinical trial. This information showed us that in GLIMPSE, MAVENCLAD had better relapse outcomes and longer treatment persistence compared to other oral DMTs, including fingolimod."

Also being presented are new data from an exploratory Phase IV CLASSIC-MS follow-up of patients (n=227) from the Phase III ORACLE-MS study which suggest early use of cladribine tablets reduced the risk of further relapse or disability progression (CDMS) in patients who experienced a first episode of neurologic attack with characteristics that put them at high risk of CDMS. Over half the patients (53.2%) treated with cladribine tablets remained relapse free compared to 28.2% of those who did not receive cladribine tablets. In patients who received cladribine tablets, 42.9% were diagnosed with CDMS in the median of 9.5 years since their last dose. In patients never treated with cladribine tablets, 70.4% were diagnosed with CDMS.

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In ORACLE-MS, patients with a first clinical demyelinating event were randomized to receive cladribine tablets 3.5 mg/kg, cladribine tablets 5.25 mg/kg or placebo. This analysis at the ACTRIMS Forum 2022 investigated the long-term efficacy in patients from the ORACLE-MS trial who had received at least one course of cladribine tablets (68.7%) or placebo (31.3%). Cladribine tablets (5.25 mg/kg) are not approved for any use in any region.

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.

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

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.

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).

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About Merck KGaA, Darmstadt, Germany
Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across healthcare, life science and electronics. Around 58,000 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 2020, Merck KGaA, Darmstadt, Germany, generated sales of € 17.5 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 EMD Serono in healthcare, MilliporeSigma in life science, and EMD Performance Materials. Since its founding 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.