News Release

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European Commission Grants Approval for Mavenclad (Cladribine Tablets)

- **First oral short-course treatment for highly active relapsing multiple sclerosis (RMS) now approved in Europe**
- **Mavenclad has shown sustained clinical efficacy for up to 4 years with a maximum of 20 days of oral treatment over 2 years**
- **Marketing authorization includes the 28 countries of the European Union (EU), with first launches in the UK and in Germany**

Darmstadt, Germany, August 25, 2017 – Merck, a leading science and technology company, today announced that the European Commission (EC) has granted marketing authorization for MAVENCLAD® 10mg (Cladribine Tablets) for the treatment of highly active relapsing multiple sclerosis* (RMS)[1] in the 28 countries of the European Union (EU) in addition to Norway, Liechtenstein and Iceland. MAVENCLAD® is the first oral short-course treatment to provide efficacy across key measures of disease activity in patients with highly active RMS, including disability progression, annualized relapse rate and magnetic resonance imaging (MRI) activity.

“Multiple Sclerosis (MS) is one of the world’s most common neurological disorders. With the approval of MAVENCLAD® in the European Union, we are pleased to offer patients and clinicians an innovative agent with a simplified dosing schedule as a new approach to managing active relapsing MS,” said Belén Garijo, CEO Healthcare and Member of the Executive Board of Merck. ”This is a pivotal change in the

* Defined as: patients with 1 relapse during the previous year and ≥ 1 T1 Gd+ lesion or ≥ 9 T2 lesions while on therapy with other DMDs; OR patients with ≥ 2 or more relapses in the previous year, whether on DMD treatment or not.

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treatment of MS which further demonstrates our unwavering commitment to advancing patient care."

MAVENCLAD®'s marketing authorization is based on more than 10,000 patient years of data with over 2,700 patients included in the clinical trial program,[2] and up to 10 years of observation in some patients. The clinical development program included data from three Phase III trials, CLARITY,[3,4] CLARITY EXTENSION[5] and ORACLE MS,[6] the Phase II ONWARD study;[7] and long-term follow-up data from the 8-year prospective registry, PREMIERE.[8] The efficacy and safety results of these studies allowed for a full characterization of the benefit-to-risk profile of MAVENCLAD®.

"This is an exciting moment and one that will change the way we treat MS," said Gavin Giovannoni, Professor of Neurology at Barts and The London School of Medicine and Dentistry, Queen Mary University of London. "MAVENCLAD® is a selective immune reconstitution therapy (SIRT) which simplifies treatment administration, by giving patients just two short annual courses of tablets in four years. Patients can benefit from the treatment over a longer period of time without having to continually take medication and without the need for frequent monitoring."

The authorization follows a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) that was received in June 2017. MAVENCLAD® is expected to become commercially available to patients in Europe by prescription within the coming months, with initial launches in Germany and UK expected as early as September 2017. In addition, Merck plans additional filings for regulatory approval in other countries, including the United States.

"Multiple Sclerosis affects more than 700,000 people across Europe and has no cure to date," said Anne Winslow, President of the European Multiple Sclerosis Platform. "New treatment options will significantly help improve the quality of life of people living with active relapsing MS."

In patients with high disease activity, post hoc analyses of the two-year Phase III CLARITY trial[4,4] demonstrated that MAVENCLAD® reduced the annualized relapse rate by 67% and the risk of 6-month confirmed EDSS progression by 82% versus

placebo. As demonstrated in the Phase III CLARITY EXTENSION[5] study, no further MAVENCLAD® treatment was required in Years 3 and 4. The comprehensive dataset has informed the posology and monitoring requirements. The most clinically relevant adverse reactions were lymphopenia and herpes zoster. Lymphocyte counts must be assessed before, and during, treatment with MAVENCLAD®. MAVENCLAD® is contraindicated in certain groups including immunocompromised patients and pregnant women.

About MAVENCLAD®
MAVENCLAD® (cladribine tablets) is approved in the European Union for the treatment of highly active relapsing multiple sclerosis* (RMS). MAVENCLAD® is a short-course oral therapy that selectively and periodically targets lymphocytes thought to be integral to the pathological process of relapsing MS (RMS). MAVENCLAD® is currently under clinical investigation and not yet approved for the treatment for any use in the United States or Canada. In August 2017, the European Commission (EC) granted marketing authorization for MAVENCLAD® for the treatment of relapsing forms of multiple sclerosis (RMS) in the 28 countries of the European Union (EU) in addition to Norway, Liechtenstein and Iceland.

The clinical development program for MAVENCLAD® includes:

- The CLARITY (CLAdRIbine Tablets Treating MS OrallY) study: a two-year Phase III placebo-controlled study designed to evaluate the efficacy and safety of MAVENCLAD® as a monotherapy in patients with RRMS.
- The CLARITY extension study: a two-year Phase III placebo-controlled study following on from the CLARITY study, designed to evaluate the safety and efficacy of MAVENCLAD® over an extended administration for four years.
- The ORACLE MS (ORAl CLadribine in Early MS) study: a two-year Phase III placebo-controlled study designed to evaluate the efficacy and safety of MAVENCLAD® as a monotherapy in patients at risk of developing MS (patients who have experienced a first clinical event suggestive of MS).
- The ONWARD (Oral Cladribine Added ON To Interferon beta-1a in Patients With Active Relapsing Disease) study: a Phase II placebo-controlled study designed primarily to evaluate the safety and tolerability of adding MAVENCLAD® treatment to patients with relapsing forms of MS, who have experienced breakthrough disease while on established interferon-beta therapy.
- PREMIERE (Prospective Observational Long-term Safety Registry of Multiple Sclerosis Patients Who Have Participated in Cladribine Clinical Studies) study: interim long-term follow-up data from the prospective registry, PREMIERE, to evaluate the safety and efficacy of MAVENCLAD®. This includes more than 10,000 patient years of data with over 2,700 patients included in the clinical trial program, and up to 10 years of observation in some patients.
- Side effects of MAVENCLAD® include a reduction in lymphocyte count, infections (including herpes zoster), and possible increased risk of malignancy. In clinical studies, 20% to 25% of the patients treated with a cumulative dose of cladribine 3.5 mg/kg over 2 years as monotherapy developed transient grade 3 or 4 lymphopenia. Patients with hypersensitivity to the product, human immunodeficiency virus (HIV), active chronic infection or malignancy, who are immunocompromised or have renal impairment, and women who are pregnant or breastfeeding should not take MAVENCLAD®. Males and females of childbearing potential must use effective contraception during MAVENCLAD® treatment and for at least six months after the last dose due to the potential risk of fetal harm.

EU Indication
MAVENCLAD® (cladribine tablets) is indicated for the treatment of adult patients with highly active relapsing multiple sclerosis (RMS) as defined by clinical or imaging features.

Important EU Safety Information
Contraindications:
MAVENCLAD® is contraindicated in patients with hypersensitivity to the active substance, human immunodeficiency virus (HIV), active chronic infection (tuberculosis or hepatitis), active malignancy, moderate to severe renal impairment (creatinine clearance <60 mL/min), and those who are pregnant and breast-feeding. MAVENCLAD® is also contraindicated in immunocompromised patients, including patients currently receiving immunosuppressive or myelosuppressive therapy.

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Special warnings and precautions for use:
The most clinically relevant adverse reactions were lymphopenia and herpes zoster.

Haematological monitoring
Decreases in neutrophil count, red blood cell count, haematocrit, haemoglobin or platelet count compared to baseline values have been observed in clinical studies, although these parameters usually remain within normal limits.

Additive haematological adverse reactions may be expected if cladribine is administered prior to or concomitantly with other substances that affect the haematological profile

Lymphocyte counts must be determined

- before initiating MAVENCLAD® in year 1,
- before initiating MAVENCLAD® in year 2,
- 2 and 6 months after start of treatment in each treatment year. If the lymphocyte count is below 500 cells/mm³, it should be actively monitored until values increase again.

Infections
Cladribine can reduce the body's immune defence and may increase the likelihood of infections. HIV infection, active tuberculosis and active hepatitis must be excluded before initiation of cladribine.
The incidence of herpes zoster was increased in patients on cladribine. If lymphocyte counts drop below 200 cells/mm³, anti-herpes prophylaxis according to local standard practice should be considered during the time of grade 4 lymphopenia. Interruption or delay of MAVENCLAD® may be considered until proper resolution of the infection.

Cases of progressive multifocal leukoencephalopathy (PML) have been reported for parenteral cladribine in patients treated for hairy cell leukaemia with a different treatment regimen.

In the clinical study data base of cladribine in MS (1,976 patients, 8,650 patient years) no case of PML has been reported. However, a baseline magnetic resonance imaging (MRI) should be performed before initiating MAVENCLAD® (usually within 3 months).

About Multiple Sclerosis (MS)
Multiple sclerosis (MS) is an autoimmune, chronic and inflammatory condition that affects the central nervous system (CNS) and is the most common, non-traumatic, disabling neurological disease in young adults. Relapsing remitting MS (RRMS) is the most common form of MS, and around 85% of people with MS are diagnosed with this type.[9] The exact cause of MS is unknown but it is thought that the body's immune system attacks myelin, disrupting the information flow along the nerves. There is currently no cure for MS, but treatments are available to help slow the course of the disease.

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About Merck
Merck is a leading science and technology company in healthcare, life science and performance materials. Around 50,000 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 2016, Merck generated sales of €15.0 billion in 66 countries.

Founded in 1668, Merck is the world's oldest pharmaceutical and chemical company. The founding family remains the majority owner of the publicly listed corporate group. Merck holds the global rights to the Merck name and brand. The only exceptions are the United States and Canada, where the company operates as EMD Serono, MilliporeSigma and EMD Performance Materials.

[1] MAVENCLAD® Summary of Product Characteristics August 2017
[2] Merck data on file

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[3] Giovannoni G, Comi G, Cook S et al. A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis. 2010 New England Journal of Medicine 362:416-426

[4] Giovannoni G et al. Sustained disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets in the CLARITY study: a post-hoc and subgroup analysis Lancet Neurol 2011; 10:329–337

[5] EU Clinical Trials Register. A Phase IIIb, Double-Blind, Placebo-Controlled, Multicenter, Parallel Group, Extension Trial to Evaluate the Safety and Tolerability of Oral Cladribine in Subjects with Relapsing-Remitting Multiple Sclerosis Who Have Completed Trial 25643 (CLARITY). Available at https://www.clinicaltrialsregister.eu/ctr-search/trial/2007-000381-20/results. Last accessed August 2017

[6] Leist T, Comi G, Cree B et al. Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): a phase 3 randomised trial. Lancet Neurol 2014; 13: 257–67

[7] EU Clinical Trials Register. A phase II, multicenter, randomized, double-blind, placebo-controlled, safety, tolerability and efficacy study of add-on Cladribine tablet therapy with Rebif New Formulation in Multiple Sclerosis Subjects with Active Disease. Available at https://www.clinicaltrialsregister.eu/ctr-search/trial/2006-003366-33/results. Last accessed August 2017

[8] Schreiner T, Miravalle A,. Current and Emerging Therapies for the Treatment of Multiple Sclerosis: Focus on Cladribine. Journal of Central Nervous System Disease. 2012; 4: 1–14