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News Release

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March 25, 2019

Cladribine Tablets Approved As The First Short-Course Oral Treatment for Relapsing Remitting Multiple Sclerosis in Switzerland

- **Cladribine tablets is now approved in 52 countries worldwide**
- **Approval brings forward new treatment option with a novel mechanism for highly active relapsing multiple sclerosis in Switzerland**
- **Approval based on extensive clinical development program capturing more than 10,000 patient years of safety data and up to 10 years of follow-up in some patients**
- **Cladribine tablets provides the possibility of up to four years of disease control with a maximum of 20 days of oral treatment administered over two years**

Darmstadt, Germany, March 25, 2019 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced that MAVENCLAD® (cladribine tablets) has been approved for the treatment of highly active relapsing remitting multiple sclerosis* (RRMS)[i] in Switzerland. Cladribine tablets is the only treatment for RRMS that provides the possibility of up to four years of disease control with a maximum of 20 days of oral treatment administered over two years.

"The Swissmedic approval of Cladribine tablets is great news for patients in Switzerland with highly active relapsing remitting MS," said Luciano Rossetti, Head of Global Research & Development for the Biopharma business of Merck KGaA,

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

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Darmstadt, Germany. ”These patients have had limited treatment options and Cladribine tablets, now approved in 52 countries worldwide, represents an important new therapy with a novel mechanism as the first short-course oral treatment for relapsing remitting MS in Switzerland.”

Cladribine tablets has demonstrated durable clinical efficacy for up to four years across key measures of disease activity, including disability progression, annualized relapse rate and magnetic resonance imaging (MRI) activity. The approval of cladribine tablets is based on 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. The clinical development program included data from three placebo-controlled Phase III trials, CLARITY (pivotal efficacy study)[ii,iii] CLARITY EXTENSION[iv] and ORACLE MS,[v] the Phase II ONWARD study;[vi] and long-term follow-up data from the 8-year prospective registry, PREMIERE.[vii] The efficacy and safety results of these studies allowed for a full characterization of the benefit-to-risk profile of cladribine tablets.

“To receive a reliably effective therapy remains the most important consideration for patients,” said Professor Ludwig Kappos, Chair Neurology, University Hospital Basel, Switzerland. “The medium and long-term treatment risks ought to be as low as possible. Last but not least the treatment should be very compatible with a normal daily life. The approval of cladribine tablets for highly active relapsing remitting multiple sclerosis by Swissmedic in Switzerland is good news because it extends the range of options for this group of MS patients with an oral treatment with proven, long-lasting effect.”

In patients with high disease activity, post hoc analyses of the two-year Phase III CLARITY trial[ii,viii] demonstrated that cladribine tablets reduced the annualized relapse rate by 67% and the risk of 6-month confirmed Expanded Disability Status Scale (EDSS) progression by 82% versus placebo. As demonstrated in the Phase III CLARITY EXT[ix] study, no further cladribine tablets treatment was required in Years 3 and 4. Cladribine tablets has a well-characterized safety profile, with up to ten years of observation in some patients and no reported cases of progressive multifocal leukoencephalopathy (PML)† in MS. The most clinically relevant adverse reactions were lymphopenia and herpes zoster. Lymphocyte counts must be

assessed before, and during, treatment with Cladribine tablets. Cladribine tablets is contraindicated in certain groups including immunocompromised patients and pregnant women.

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About Cladribine tablets

Cladribine tablets (marketed as MAVENCLAD® outside the U.S.) is an investigational oral therapy studied as a short 8-10 day per year treatment regimen that is thought to preferentially target lymphocytes which may be integral to the pathological process of relapsing MS (RMS). Cladribine tablets is currently undergoing FDA review and is not approved for the treatment for any use in the United States. Cladribine tablets has been approved in more than 50 countries, including the European Union (EU), Canada, and Australia, for various relapsing MS indications.

The clinical development program for cladribine tablets 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 cladribine tablets as a monotherapy in patients with RRMS.
- The CLARITY extension study: a Phase III placebo-controlled study following on from the CLARITY study, which evaluated the safety and exploratory efficacy of cladribine tablets over two additional years beyond the two-year CLARITY study, according to the treatment assignment scheme for years 3 and 4.
- 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 cladribine tablets 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 cladribine tablets 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) study: a long-term observational follow-up safety registry of MS patients who participated in cladribine tablets clinical studies.

In the two-year CLARITY study, the most commonly reported adverse event (AE) in patients treated with Cladribine tablets was lymphopenia (26.7% with cladribine tablets and 1.8% for placebo). The incidence of infections was 48.3% with Cladribine tablets and 42.5% with placebo, with 99.1% and 99.0% respectively rated mild-to-moderate by investigators. Adverse Events reported in other clinical studies were similar.

Swiss Indication and Important Safety Information
Mavenclad® (**10 mg** cladribine)
I: Adult patients with highly active relapsing-remitting multiple sclerosis (MS), as defined by clinical or imaging findings. **PO:** Dose of 3.5 mg/kg body weight over 2 years, administered as 1 treatment phase of 1.75 mg/kg per year. **CI:** Hypersensitivity to cladribine or any of the excipients. Infection with the human immunodeficiency virus (HIV). Severe active infections, active chronic infection (e.g. tuberculosis or hepatitis). Initiation of treatment in immunocompromised patients. Existing active malignant disease. History of progressive multifocal leukoencephalopathy. Moderate or severe impairment of renal function. Children and adolescents under 18 years. Pregnancy and breast-feeding. **W:** *General*: Not recommended in patients with inactive disease or stabilised on established therapy. No more than 2 annual treatment phases within 4 years. *Haematological monitoring*: The lymphocyte count must be determined before the start of treatment with Mavenclad in year 1 and year 2, as well as 2 and 6 months after initiation of treatment in each year of treatment. *Infections*: Cladribine can weaken the body's immune system and potentially increase the likelihood of infection. Patients with lymphocyte counts below

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500 cells/mm^3 must be actively monitored for signs and symptoms of infection, especially herpes zoster. *Malignant disease*: Cladribine interferes with DNA synthesis and has an immunosuppressive effect. *Contraception*: Reliable contraceptive methods must be used during treatment with cladribine and for at least 6 months after the last dose. *Blood transfusions*: In patients requiring blood transfusions, irradiation of the cellular blood components is recommended prior to transfusion. *Switching to cladribine and from cladribine to other medicinal products*: Before starting treatment with Mavenclad, the mechanism of action and duration of action of the other medicinal product should be taken into account. *Renal disease*: Mavenclad must not be used in cases of moderate or severe impairment of renal function. *Hepatic disease*: Mavenclad is not recommended in cases of moderate or severe impairment of liver function. *Fructose intolerance*: Patients with fructose intolerance should not take Mavenclad. **IA:** Mavenclad contains hydroxypropylbetadex, which may be able to form complexes with other medicinal products and hence lead to increased bioavailability of these medicinal products. *Haematotoxic or immunosuppressive medicines* (methotrexate, cyclophosphamide, ciclosporin, azathioprine, corticosteroids). *Other disease-modifying drugs*. *Haematotoxic medicines* (carbamazepine). *Live vaccines and live attenuated vaccines*. *Potent inhibitors of ENT1, CNT3 and BCRP transporters* (*such as* dilazep, nifedipine, nimodipine, cilostazol, sulindac, reserpine). *Potent inducers of BCRP and P-gp transporters (e.g.* corticosteroids and rifampicin, St. John's wort). *Hormonal contraceptives*. Most common **UE**: lymphopenia, oral herpes, dermatomal herpes zoster, reduction in neutrophil count, rash, alopecia. **P:** Mavenclad 10 mg: 1, 4 or 6 tablets. [A] For detailed information, see www.swissmedicinfo.ch. FEB19

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 and Multiple Sclerosis
For more than 20 years, Merck KGaA, Darmstadt, Germany has been relentlessly focused on understanding the journey people living with MS face in order to create a meaningful, positive experience for them and the broader MS community. However, there is still much that is unknown about this complex and unpredictable disease. Merck KGaA, Darmstadt, Germany is digging deeper to advance the science and reconstruct a new understanding of MS, inside and out. We are committed to delivering solutions that improve the lives of all those affected by MS.

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 KGaA, Darmstadt, Germany operate as EMD Serono in healthcare, MilliporeSigma in life science, and EMD Performance Materials.

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[i] MAVENCLAD® Summary of Product Characteristics February 2019
[ii] 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
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[viii] Giovannoni G, Sorensen P, Cook S et al. Efficacy of Cladribine Tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: A post hoc analysis of the CLARITY study. 2018 Multiple Sclerosis Journal 1-9 [Epub ahead of print]

[ix] Giovannoni G, Sorensen P, Cook S et al. Safety and efficacy of cladribine tablets in patients with relapsing–remitting multiple sclerosis: Results from the randomized extension trial of the CLARITY study. 2018 Multiple Sclerosis Journal 24(12) 1594-1604