News Release

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Merck KGaA, Darmstadt, Germany Receives First Approval for Cladribine Tablets in Middle East & Africa Region

- **First oral short-course treatment for highly active relapsing multiple sclerosis (RMS) approved in United Arab Emirates**
- **Mavenclad has shown sustained clinical efficacy for up to 4 years with a maximum of 20 days of oral treatment over 2 years**

Darmstadt, Germany, April 9, 2018 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced that the United Arab Emirates Ministry of Health and Prevention, has approved the registration of MAVENCLAD® (cladribine tablets) for the treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features. This marks the first approval for MAVENCLAD® in the Middle East & Africa region and following local regulatory processes, the product is expected to be available in the coming months. The United Arab Emirates (UAE) is the first country in the region to approve the adoption of this therapy, which is a direct outcome of accelerated processes by the Ministry of Health and Prevention aimed at making the latest advances and best quality of healthcare services and medications available within the country.

"The accelerated processes implemented by the Ministry of Health and Prevention allow for significant advancements in care, we applaud them for fostering an environment in which patients gain expedited access to innovations such as Mavenclad," said Rehan Verjee, Chief Marketing and Strategy Officer at the Biopharma business of Merck KGaA, Darmstadt, Germany.

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News Release

Cladribine Tablets is the first oral short-course treatment to provide efficacy across key measures of disease activity in patients with highly active relapsing MS, including disability progression, annualized relapse rate and magnetic resonance imaging (MRI) activity. The approval of MAVENCLAD® is based on more than 10,000 patient years of data with over 2,700 patients included in the clinical trial program,[1] and up to 10 years of observation in some patients. The clinical development program included data from three Phase III trials, CLARITY,[2,3] CLARITY EXTENSION[4] and ORACLE MS,[5] the Phase II ONWARD study;[6] and long-term follow-up data from the 8-year prospective registry, PREMIERE.[7] The efficacy and safety results of these studies allowed for a full characterization of the benefit-to-risk profile of Cladribine Tablets.

Cladribine Tablets is thought to be an immune reconstitution therapy[8,9] that selectively targets B & T lymphocytes followed by a distinct pattern of lymphocyte reconstitution, without continuous suppression of the immune system.[10]

In patients with high disease activity, post hoc analyses of the two-year Phase III CLARITY trial[3,4] 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 EXTENSION[4] study, no further Cladribine Tablets 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 Cladribine Tablets. In the UAE, Cladribine Tablets is contraindicated in certain groups including immunocompromised patients and pregnant women.

About Cladribine Tablets
Cladribine Tablets is currently under clinical investigation and not yet approved for any use in the United States. Cladribine Tablets is approved as MAVENCLAD® in the 28 countries of the European Union (EU) in addition to Norway, Liechtenstein, Iceland, Israel, United Arab Emirates and Argentina for the treatment of highly active relapsing multiple sclerosis (RMS). It is approved in Canada and Australia for the treatment of relapsing-remitting multiple sclerosis (RRMS). Cladribine Tablets is a short-course oral therapy that is thought to selectively targets lymphocytes thought to be integral to the pathological process of relapsing MS (RMS).

The clinical development program for Cladribine Tablets includes:

News Release

- 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®

The clinical development program of Cladribine Tablets in MS comprises more than 10,000 patient years of data with over 2,700 patients included in the clinical trial program, and more than 10 years of observation in some patients.

Cladribine Tablets 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. Cladribine Tablets is also contraindicated in immunocompromised patients, including patients currently receiving immunosuppressive or myelosuppressive therapy.

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 Cladribine Tablets in year 1, before initiating Cladribine Tablets 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 Tablets 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 Cladribine Tablets 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
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.

News Release

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About Merck KGaA, Darmstadt, Germany
Merck KGaA, Darmstadt, Germany, 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 2017, Merck KGaA, Darmstadt, Germany, generated sales of € 15.3 billion in 66 countries.

Founded in 1668, Merck KGaA, Darmstadt, Germany, is the world's oldest pharmaceutical and chemical company. The founding family remains the majority owner of the publicly listed corporate group. 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 company operates as EMD Serono, MilliporeSigma and EMD Performance Materials.

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