Mavenclad (Cladribine Tablets) Receives First Approval in Latin America

Merck today announced that the Argentinian Administration of Medicines, Food and Medical Technology (ANMAT), has approved the registration of MAVENCLAD® (cladribine tablets) for the treatment of adult ...

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- **First oral short-course treatment for highly active relapsing multiple sclerosis (RMS) now approved in Argentina**
- **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, February 26, 2018 – Merck, a leading science and technology company, today announced that the Argentinian Administration of Medicines, Food and Medical Technology (ANMAT), 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 Latin America and following local regulatory processes, the product is expected to be available in the coming months.

"Having a new MS treatment approved in Argentina is very motivating," said Dr. Jorge Correale M.D., the Head of Neuroimmunology and Demyelinating Diseases at the Institute for Neurological Research Dr. Raúl Carrea. "Mavenclad allows the patient's immune system to go through a selective immune reconstitution, similar to a reset, and the treatment mechanism is simple because it does not require frequent administration or monitoring."

MAVENCLAD® 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,[i] and up to 10 years of observation in some patients. The clinical development program included data from three Phase III trials, CLARITY,[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 MAVENCLAD®.

"We are pleased the Argentinian Administration of Medicines, Food and Medical Technology has approved Mavenclad," said Rehan Verjee, Chief Marketing and Strategy Officer at the Biopharma business of Merck. "Our goal is to ensure fast access to patients who may benefit from this innovative therapy and we will be working with payers on obtaining reimbursement as a next step."

MAVENCLAD® is a selective immune reconstitution therapy[viii],[ix] which simplifies treatment administration by giving patients just 2 short annual courses of tablets with a maximum of 20 days of treatment over 2 years providing a lasting treatment benefit up to 4 years. MAVENCLAD® works by selectively targeting B & T lymphocytes followed by a distinct pattern of lymphocyte reconstitution, without continuous suppression of the immune system.[x]

In patients with high disease activity, post hoc analyses of the two-year Phase III CLARITY trial[3,4] demonstrated that MAVENCLAD® 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 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.

[1] Merck data on file

[2] Giovannoni G, Comi G, Cook S et al. A Placebo-Controlled Trial of 1Oral Cladribine for Relapsing Multiple Sclerosis. 2010 New England Journal of Medicine 362:416-426

[3] 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

[4] 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

[5] 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

[6] 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

[7] 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

[8] Giovannoni G. Personalized medicine in multiple sclerosis. 2017 Neurodegenerative Disease Management; 7 (6s) 13-17

[9] Giovannoni G. Cladribine to Treat Relapsing Forms of Multiple Sclerosis. Neurotherapeutics. November 2017; DOI 10.1007/s13311-017-0573-4

[10] MAVENCLAD™ Product Monograph. November 2017

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About MAVENCLAD®

MAVENCLAD® (cladribine tablets) is approved in the 28 countries of the European Union (EU) in addition to Norway, Liechtenstein, Iceland, Isreal and Argentina for the treatment of highly active relapsing multiple sclerosis (RMS). MAVENCLAD® is approved in Canada and Australia for the treatment of relapsing-remitting multiple sclerosis (RRMS). MAVENCLAD® is a short-course oral therapy that selectively 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.

The clinical development program for MAVENCLAD® includes: