Mavenclad® (cladribine) – New drug approval

- On March 29, 2019, the FDA announced the approval of EMD Serono's Mavenclad (cladribine), for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Due to 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 MS.
    - Mavenclad is not recommended for use in patients with clinically isolated syndrome because of its safety profile.
- MS is a chronic, inflammatory, autoimmune disease of the central nervous system that affects around 2.3 million people worldwide. For most people, MS starts with a relapsing-remitting course, in which episodes of worsening function (relapses) are followed by recovery periods (remissions). These remissions may not be complete and may leave patients with some degree of residual disability.
- Many patients with MS experience some degree of persistent disability that gradually worsens over time. In some patients, disability may progress independent of relapses, a process termed secondary progressive MS (SPMS). In the first few years of this process, many patients continue to experience relapses, a phase of the disease described as **active** SPMS.
    - Active SPMS is one of the relapsing forms of MS, and drugs approved for the treatment of relapsing forms of MS can be used to treat active SPMS.
- Mavenclad, a cytotoxic drug, is the first short-course oral therapy for the treatment of adults with relapsing-remitting disease (RRMS) and SPMS. The mechanism by which cladribine exerts its therapeutic effects in patients with MS 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.
    - Cladribine is also available as an intravenous infusion. This formulation is only approved for the treatment of active Hairy Cell Leukemia.
- The efficacy of Mavenclad was established in a double-blind study in 1,326 patients with relapsing forms of MS. Patients were randomized to receive placebo or a cumulative oral dosage of Mavenclad 3.5 mg/kg or Mavenclad 5.25 mg/kg body weight over the 96-week study period in 2 treatment courses. The primary outcome was the annualized relapse rate (ARR).
    - The ARR was 0.14 and 0.33 for patients receiving Mavenclad 3.5 mg/kg and placebo, respectively ($p < 0.001$). The relative risk reduction was 58%.
    - The proportion of patients without a relapse was 81% vs. 63% for Mavenclad 3.5 mg/kg and placebo, respectively (nominal $p < 0.05$).
    - The Mavenclad 5.25 mg/kg cumulative dose did not add any clinically meaningful benefit, but was associated with a higher incidence in grade 3 lymphopenia or higher.
- Mavenclad is contraindicated in:
    - Patients with current malignancy
    - Pregnant women and in women and men of reproductive potential who do not plan to use effective contraception during Mavenclad dosing and for 6 months after the last dose in each treatment course; Mavenclad may cause fetal harm
    - Patients infected with the human immunodeficiency virus

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- Patients with active chronic infections (eg, hepatitis or tuberculosis)
- Patients with a history of hypersensitivity to cladribine
- Women intending to breastfeed on a Mavenclad treatment day and for 10 days after the last dose

- Warnings and precautions of Mavenclad include malignancies, risk of teratogenicity, lymphopenia, infections, hematological toxicity, risk of graft-versus-host disease with blood transfusions, liver injury, hypersensitivity, and cardiac failure.

- The most common adverse reactions (> 20%) with Mavenclad use were upper respiratory tract infection, headache, and lymphopenia.

- The recommended cumulative dosage of Mavenclad is 3.5 mg/kg body weight administered orally and divided into 2 yearly treatment courses (1.75 mg/kg per treatment course). Each treatment course is divided into 2 treatment cycles:

  - Administration of first treatment course:
    - First course/first cycle: start any time
    - First course/second cycle: administer 23 to 27 days after the last dose of first course/first cycle
  - Administration of second treatment course
    - Second course/first cycle: administer at least 43 weeks after the last dose of first course/second cycle
    - Second course/second cycle: administer 23 to 27 days after the last dose of second course/first cycle
  - The cycle dosage should be administered as 1 or 2 tablets once daily over 4 or 5 consecutive days. More than 2 tablets daily should not be administered.
  - Following the administration of 2 treatment courses, additional Mavenclad treatment should not be administered during the next 2 years. Treatment during these 2 years may further increase the risk of malignancy. The safety and efficacy of reinitiating Mavenclad more than 2 years after completing 2 treatment courses has not been studied.
  - Refer to the Mavenclad drug label for additional dosing and administration recommendations.

- EMD Serono's launch plans for Mavenclad are pending. Mavenclad will be available as 10 mg tablets.