PDL DRUG REVIEW

Proprietary Name: Mavenclad®
Common Name: cladribine
PDL Category: Multiple Sclerosis Agents

Comparable Products	Preferred Drug List Status
Aubagio	Preferred with Conditions
Gilenya	Preferred with Conditions
Tecfidera	Preferred with Conditions

Summary

Pharmacology/Usage: Cladribine, the active ingredient of Mavenclad®, is a nucleoside metabolic inhibitor. The mechanism by which it 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.

Indication: For the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of 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 (CIS) because of its safety profile.

There is no pregnancy category for this medication; however, the risk summary indicates that Mavenclad® is contraindicated in pregnant women and in females and males of reproductive potential who do not plan to use effective contraception. There are no adequate data on the developmental risk associated with use in pregnant women. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Tablets: 10mg. Swallow whole without chewing

Recommended Dosage: The following are recommended assessments prior to starting each Mavenclad® treatment course:

- Following standard cancer screening guidelines;
- Exclude pregnancy prior to treatment in females of reproductive potential;
- Obtain a CBC with differential including lymphocyte count before starting the 1st treatment course, before starting the 2nd treatment course, 2 and 6 months after start of treatment in each course (if the lymphocyte count at month 2 is below 200 cells per microliter, monitor monthly until month 6), and periodically thereafter and when clinically indicated (lymphocytes must be within normal limits before starting the first treatment course and at least 800 cells per microliter before initiating the second treatment course. If necessary, delay the second treatment course for up to 6 months to allow for recovery of lymphocytes to at least 800 cells per microliter. If this recovery takes more than 6 months, the patient should not receive further treatment with Mavenclad®);
- Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels;
- Infections (exclude HIV infection; perform TB screening; screen for hepatitis B and C; evaluate for acute infection and consider a delay in Mavenclad® treatment until any acute infection is fully controlled; vaccination of patients who are antibody-negative for varicella zoster virus is recommended prior to

initiation of Mavenclad®; administer all immunizations per immunization guidelines prior to starting Mavenclad® and administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting Mavenclad®; and obtain a baseline (within 3 months) MRI prior to the first treatment course because of the risk of progressive multifocal leukoencephalopathy (PML)).

The recommended cumulative dosage of Mavenclad® is 3.5mg per kg PO and divided into 2 yearly treatment courses (1.75mg per treatment course). Each treatment course is divided into 2 treatment cycles. With the first treatment course, the first course/first cycle can start anytime while the first course/second cycle should be administered 23 to 27 days after the last dose of the first course/first cycle. With the second treatment course, the first cycle should be administered at least 43 weeks after the last dose of the first course/second cycle while the second course can be administered 23 to 27 days after the last dose of the second course/first cycle. The use of Mavenclad® in patients weighing less than 40kg has not been investigated. Administer the cycle dosage as 1 or 2 tablets once daily over 4 to 5 consecutive days. After the administration of 2 treatment courses, do not administer additional Mavenclad® treatment 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.

Mavenclad® is a cytotoxic drug. Follow applicable special handling and disposal procedures. Mavenclad® is an uncoated tablet and must be swallowed immediately once removed from the blister. If a tablet is left on a surface or if a broken or fragmented tablet is release from the blister, the area must be thoroughly washed with water. Avoid prolonged contact with the skin.

It is recommended to administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter. However, separate administration of Mavenclad® and any other oral drugs by at least 3 hours during the 4 to 5 day Mavenclad® treatment cycles.

Dose adjustments are not required with mild renal or mild hepatic impairment; however, Mavenclad® is not recommended in patients with moderate to severe renal and in patients with moderate to severe hepatic impairment.

Drug Interactions: Concomitant use of Mavenclad® with the following is not recommended: with myelosuppressive or other immunosuppressive drugs (immunomodulatory, immunosuppressive, or myelosuppressive drugs) and with interferon-beta. Concomitant use of Mavenclad® with antivirals and antiretroviral agents should be avoided. It is recommended to consider a possible decrease in cladribine efficacy if potent BCRP (e.g. corticosteroids) or P-gp (e.g. rifampicin, St. John's Wort) transporter inducers are co-administered. Women using systemically acting hormonal contraceptives should add a barrier method during Mavenclad® dosing and for at least 4 weeks after the last dose in each treatment course. It is recommended to monitor hematological parameters with the concomitant use of Mavenclad® with hematotoxic drugs. Last, it is recommended to avoid co-administration of potent ENT1, CNT3, or BCRP transport inhibitors (e.g. ritonavir, eltrombopag, curcumin, cyclosporine, nifedipine, nimodipine, cilostazol, sulindac, dipyridamole, or reserpine) during the 4 to 5 day Mavenclad® treatment cycles. If this is not possible, consider selection of alternative concomitant drugs with no or minimal ENT1, CNT3, or BCRP transporter inhibiting properties. If this is not possible, dose reduction to the minimum mandatory dose of drugs containing these compounds, separation in the timing of administration, and careful patient monitoring is recommended.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Mavenclad®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than placebo.* The most frequently reported adverse events included upper respiratory tract infection (6%), headache (6%), lymphopenia (22%), nausea (1%), back pain (2%), arthralgia and arthritis (2%), insomnia (2%), bronchitis (2%), hypertension (2%), fever (2%), and depression (2%).

Mavenclad® has a box warning regarding malignancies and risk of teratogenicity. Treatment with Mavenclad® may increase the risk of malignancy, and use is contraindicated in patients with current malignancy. In patients with prior malignancy or with increased risk of malignancy, assess the benefits and risks of the use of Mavenclad® on an individual patient basis. Follow standard cancer screening guidelines in patients with Mavenclad®. In addition, Mavenclad® is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception because of the potential for fetal harms. Malformations and embryo-

lethality occurred in animals. Exclude pregnancy before the start of treatment with Mavenclad® in females of reproductive potential. Advise females and males of reproductive potential to use effective contraception during Mavenclad® treatment and for 6 months after the last dose in each treatment course. Stop Mavenclad® if the patient becomes pregnant.

Mavenclad® causes a dose-dependent reduction in lymphocyte count. Additive hematological adverse reactions may be expected if Mavenclad® is administered prior to or concomitantly with other drugs that affect the hematological profile. Obtain a CBC with differential including lymphocyte count prior to, during, and after treatment. In addition to lymphopenia, decreases in other blood cells and hematological parameters have been reported with Mavenclad® in clinical studies. Mild to moderate decreases in neutrophil counts were seen with Mavenclad® vs placebo (27% vs 13%, respectively) and severe decreases in neutrophil counts were also seen (3.6% vs 2.8%, respectively). Decreases in hemoglobin levels were seen more with Mavenclad® vs placebo (26% vs 19%). Decreases in platelet counts were generally mild and seen in 11% treated with Mavenclad® vs 4% with placebo. Obtain a CBC with differential prior to, during, and after treatment with Mavenclad®.

Mavenclad® can reduce the body's immune defense and may increase the likelihood of infections. Infections occurred in 49% of those treated with Mavenclad® vs 44% treated with placebo in clinical trials. The most frequent serious infections in those treated with Mavenclad® included herpes zoster and pyelonephritis. HIV infection, active TB, and active hepatitis must be excluded before the start of each treatment course and consider a delay in starting treatment in patients with an acute infection until the infection is fully controlled. Progressive Multifocal Leukoencephalopathy (PML) has not been reported in clinical studies of cladribine in patients with MS; however, in patients treated with parenteral cladribine for oncologic indications, cases of PML have been reported in the postmarketing setting. Obtain a baseline (within 3 months) MRI before starting the first treatment course of Mavenclad®. At the first sign or symptom suggestive of PML, withhold Mavenclad® and perform an appropriate diagnostic evaluation.

Transfusion-associated graft-versus-hosts disease has been observed rarely after transfusion of non-irradiated blood in patients treated with cladribine for non-MS treatment indications. In patients who require blood transfusion, irradiation of cellular blood components is recommended prior to administration to decrease the risk of transfusion-related graft-versus-host disease. Consultation with a hematologist is advised.

Liver injury considered related to treatment was reported in clinical studies with Mavenclad® as compared with placebo (0.3% vs 0%, respectively). Onset had a range of a few weeks to several months after the start of treatment. Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to the first and second treatment course. If a patient develops clinical signs, including unexplained liver enzyme elevations or symptoms suggestive of hepatic dysfunction, promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with Mavenclad®, as appropriate.

In clinical trials, one Mavenclad®-treated patient experienced life-threatening acute cardiac failure with myocarditis, which improved after about 1 week. Cases of cardiac failure have also been reported with parenteral cladribine used for treatment indications other than MS.

Contraindications: In patients with current malignancy; in 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; in patients infected with the human immunodeficiency virus (HIV); in patients with active chronic infections (e.g. hepatitis or tuberculosis); in patients with a history of hypersensitivity to cladribine; in women intending to breastfeed on a Mavenclad® treatment day and for 10 days after the last dose.

Manufacturer: EMD Serono Inc

Analysis: The efficacy of Mavenclad® was demonstrated in a 96-week randomized, double-blind, placebo-controlled clinical study in patients with relapsing forms of MS. Patients were required to have at least 1 relapse in the previous 12 months. The median age was 39 years (range 18 to 65 years) and the female to male ratio was 2:1. The mean duration of MS prior to study enrollment was 8.7 years, and the median baseline neurological disability based on the Expanded Disability Status Scale (EDSS) score across all treatment groups was 3.0. In addition, more than two-thirds of the patients were treatment-naïve for drugs used to treat relapsing forms of MS.

Included patients (N=1,326) were randomized to either placebo (N=437) or a cumulative oral dosage of Mavenclad® 3.5mg per kg (N=433) or 5.25mg per kg (N=456) over a 96-week period in 2 treatment courses. The primary outcome was annualized relapse rate (ARR). Additional outcomes assessed included the proportion with confirmed disability progression, the time to first qualifying relapse, the mean number of MRI T1 Gadolinium-enhancing (Gd+) lesions, and new or enlarging MRI T2 hyperintense lesions. Disability progression was measured in terms of a 3-month sustained change in EDSS score of at least 1 point, if baseline EDSS score was between 0.5 and 4.5, inclusively, or at least 1.5 points if the baseline EDSS score was 0, or at least 0.5 point if the baseline EDSS score was at least 5, over a period of at least 3 months. Results suggested that Mavenclad® 3.5mg per kg significantly lowered the annualized relapse rate. Results can be seen in the table below, which was adapted from the prescribing information.

Endpoints	Mavenclad 3.5mg per kg (N=433)	Placebo (N=437)
Clinical Endpoints		
Annualized Relapse Rate (ARR)	0.14*	0.33
Relative reduction in ARR	58%	
Proportion of patients without relapse	81%^	63%
Time to 3-month confirmed EDSS progression, HR	0.67^	
Proportion with 3-month EDSS progression	13%	19%
MRI Endpoints		
Median number of active T1 Gd+ lesions	0*	0.33
Median number of active T2 lesions	0*	0.67

* p<0.001 compared to placebo; ^ nominal p<0.05 compared to placebo

Place in Therapy: Mavenclad® is an oral tablet indicated for the treatment of relapsing forms of MS, to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of 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 (CIS) because of its safety profile. Compared to placebo in a phase 3 study, Mavenclad® significantly lowered the annualized relapse rate.

There is no evidence at this time that Mavenclad® is safer than the currently preferred, more cost-effective medications. Furthermore, Mavenclad® is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternative drug indicated for the treatment of MS due to its safety profile. It is therefore recommended that Mavenclad® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement:
- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☒ **Refer to DUR for PA Criteria**

References

[1]Mavenclad [package insert]. Rockland, MA: EMD Serono, Inc; 2019.