Transcript Details
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Expert Insights on an Oral Treatment for Relapsing Forms of MS

Announcer:
Welcome to ReachMD.

This promotional program titled “Expert Insights on an Oral Treatment for Relapsing Forms of MS” is sponsored by EMD Serono, Inc. The speakers in this video are not employees of EMD Serono but have been retained to present on behalf of EMD Serono. The information presented in this video is consistent with the prescribing information for MAVENCLAD® (cladribine) tablets, however, is not intended to replace the prescribing information.

MAVENCLAD (cladribine) tablets is indicated 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.

Limitations of Use: MAVENCLAD is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile.

WARNING: MALIGNANCIES and RISK OF TERATOGENICITY

- **Malignancies:** MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy; evaluate the benefits and risks on an individual basis for patients with prior or increased risk of malignancy.
- **Risk of Teratogenicity:** 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 risk of fetal harm.

CONTRAINDICATIONS:

- Patients with current malignancy.
- Pregnant women, and women and men of reproductive potential who do not plan to use effective contraception during and for 6 months after the last dose in each treatment course. May cause fetal harm.
- Patients with human immunodeficiency virus (HIV).
- Patients with active chronic infections (e.g., hepatitis or tuberculosis).
- Patients with a history of hypersensitivity to cladribine.
- Women intending to breastfeed while taking MAVENCLAD tablets and for 10 days after the last dose.

Please stay tuned for Important Safety Information at the end of this video, and see full Prescribing information, including boxed WARNING, and Medication Guide at www.mavenclad.com.

Here’s your host Dr. Jennifer Caudle.

Dr. Caudle:
Coming to you from the 2019 CMSC Annual Meeting in Seattle, Washington, I’m your host, Dr. Jennifer Caudle. And joining me to discuss MAVENCLAD® (cladribine) tablets, a treatment option for relapsing forms of multiple sclerosis approved for use in the United States in 2019, are Dr. Timothy West, Dr. Donald Negroski, Mary Kay Fink and Dr. Elaine Edmonds. Here is what they had to share with us.

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So, to start off, Dr. West, can you tell us a little bit about some of the key challenges that you and your patients face in the treatment of MS?

Dr. West:
Thank you for inviting me here, and I'm excited to talk about this. I think in the world of multiple sclerosis, one of the biggest problems we face is that everybody's course through the disease is a little bit different. It's a pretty heterogenous illness, and that means that a one-size-fits-all approach just doesn't work very well. Each individual is going to have a different presentation. And one of the beautiful things about the world of multiple sclerosis over the past few years is that our ability to treat has expanded. We have a number of options. But again, given that things are changing, and even just in the life of an MS patient, the choices of which medicine to pick can be different at different times in life. It's a large challenge for us to try to find that right medicine for that person.

Dr. Caudle:
For those who are not familiar with this treatment option, Mary Kay, can you provide some background about what Mavenclad is?

Mary Kay Fink:
Mavenclad is the first FDA-approved, short-term oral treatment for relapsing forms of MS. We know that it is FDA approved for relapsing forms of MS, which include relapsing-remitting MS and active secondary progressive MS. We also have in our label that says, because of the safety profile, Mavenclad should be used for people that may have intolerability or a need to switch off of another disease-modifying agent. That being said, it is not indicated for clinically isolated syndrome of MS. But we're thrilled to have a short-term course of treatment for MS that's oral in nature.

Announcer:
MAVENCLAD is the first oral MS treatment to provide two years of proven efficacy with a maximum of 20 days of oral treatment, during a two-year period. See Prescribing Information for Screening and Monitoring recommendation before, during and after treatment.

Dr. Caudle:
So, now can you tell us about how MAVENCLAD works?

Dr. West:
So, Mavenclad has an interesting proposed mechanism of action. When it comes to any of the medicines that we have, the actual way in which these works is not fully elucidated, but what is thought to happen in this particular medicine is that its action is through lymphocytes. Cladribine is actually a prodrug, which is then brought into the cells and then activated by kinases within the cells which then, once they are activated, they build up. Now, generally speaking, within a cell, when these build up it causes cell death. There is usually a way for your cell to salvage that pathway through this thing called adenosine deaminase and break it down. That is actually not —doesn't function in cladribine. One of the things, the ways that it works, is that there is this chlorine molecule added to it which makes it resistant to this breakdown process. As a result, it does build up, and then it leads to cell death. And what that means in the world of the lymphocytes is that the B-cells and the T-cells, which we know are causing a lot of the injury in multiple sclerosis, are the ones that die. What's also interesting about this is that you have to have a ratio that's more leaning towards the kinase being higher than the phosphatase for it to activate. That tends to be found mostly in these lymphocytes—also seen in a couple of other immune cells.

Announcer:
MAVENCLAD causes a dose-dependent reduction in lymphocyte count. In clinical studies, 87% of MAVENCLAD-treated patients experienced lymphopenia. In addition to lymphopenia, decreases in other blood cells and hematological parameters have been reported with MAVENCLAD in clinical studies. In general, mild to moderate decreases in neutrophil counts, hemoglobin levels, and platelet counts were observed. Severe decreases in neutrophil counts were observed in 3.6% of MAVENCLAD-treated patients, compared to 2.8% of placebo patients. Obtain complete blood count (CBC) with differential including lymphocyte count before and during treatment, periodically thereafter, and when clinically indicated .

Dr. Caudle:
Can you tell us about the efficacy results of Mavenclad as demonstrated in clinical trials?

Dr. Negroski:
So the name of the pivotal phase III clinical trial was CLARITY. It was a 2-year trial in patients with relapsing-remitting multiple sclerosis. The baseline demographics in that trial were patients between the ages of 18 and 65. They had MS for about 7 point—or actually 8.7 years. Their extended disability status scale was 3 on a scale of 0 to 10. Patients were administered 2 doses of Mavenclad, a higher dose and the current FDA-approved dose of 3.5 mg per kilogram and followed over a 2-year period compared to placebo. The outcome measurements that they looked at were basically common outcome measurements in clinical trials. One is the annualized relapse rate reduction. At 2 years there was a 58% reduction of annualized relapse rate. Another endpoint that they looked at is 3-month confirmed

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disability. So there was a 33% reduction of 3-month confirmed disability compared to placebo. And a third parameter that they looked at is MRI. The MRI parameter was statistically significant with Gd-positive lesions as well as new active or enlarging T2 lesions, both using statistics called a median and a mean duration.

Announcer:
As demonstrated in clinical trials, the most common adverse reactions, with an incidence of >20% for MAVENCLAD, are upper respiratory tract infection, headache and lymphopenia.

Dr. Negroski:
They also did a post-hoc analysis of secondary progressive MS patients using an EDSS of 3.5 as a surrogate marker or a proxy marker of secondary progressive MS. So, if you looked at the initial clinical trial, about 40% of those patients had active secondary progressive disease, and looking at their annualized relapse rate, it was 57% against placebo. Another post-hoc analysis looked at NEDA, no evidence of disease activity, looking at patients that had no relapses, no new MRI activity, both with Gd-positive and active T2 lesions, as well as no increased 3-month disability, and the statistics with cladribine was 44% of patients reached NEDA and only 16% of placebo patients reached NEDA.

Announcer:
An EDSS score of >/= 3.5 was used as a proxy marker for active secondary progressive MS.

Dr. Caudle:
And now that we've discussed the efficacy profile of Mavenclad, can you share more information about the safety profile for our audience? That's going to be very important.

Dr. Negroski:
So there is a box warning for MAVENCLAD in terms of malignancy and risk of teratogenicity, which is very important to understand. Patients that should not take MAVENCLAD are a few. One is if you have an active malignancy. That's an exclusionary criteria. If there's an active infection such as tuberculosis or hepatitis, if the patient has a hypersensitivity to the ingredients or the drug itself, if the patient is pregnant or planning to become pregnant on the drug and not use effective birth control, that is a contraindication as well.

Dr. Caudle:
Sure

Dr. Negroski:
So there are some contraindications to the drug, and before a patient is started, they need to have those things checked in terms of an HIV test, hepatitis screening, TB testing, a blood count including a differential and absolute lymphocyte count and a liver profile. They should also have an MRI of the brain within 3 months of starting.

Mary Kay Fink:
Again, if we think about the population of MS, many patients are women, and again, they may be of childbearing age, so I think, again, counseling about pregnancy and family planning is very, very important. We do not want patients to be pregnant on cladribine, so I'm going to exclude pregnancy before I would start the medication. But additionally, I'm going to talk to them about family planning. I'm going to talk to them about contraception and what is effective contraception. I will counsel both my female and male patients about contraception.

Dr. Caudle:
Sure.

Mary Kay Fink:
They should stay on effective contraception through the 2-year treatment course and for 6 months after the last dose of MAVENCLAD. Also, breastfeeding is contraindicated with MAVENCLAD.

Dr. Caudle:
Okay.

Mary Kay Fink:
So we have to pay attention to that and talk to our female patients about breastfeeding in either initiation of MAVENCLAD or if they come off and choose to have a pregnancy later on.

Dr. Caudle:
As a healthcare practitioner and provider, let's talk about sort of like the big picture. What role do you really see for Mavenclad in the MS

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treatment landscape? What do you see for this drug?

Dr. Edmonds:
Well, as I said earlier, we have patients who are either not tolerating or not benefitting from the medications that they're on, even though we have many medications to choose from, so those patients who either aren't tolerating or aren't benefitting, this provides them with an alternative. The way that it's dosed, it's given for 4 to 5 days, and then a month later another 4 to 5 days, and they don't get a second dose until 1 year later. And it's also recommended that we don't treat them in years 3 and 4 because there's a potential for increase in rates of malignancy.

Announcer:
Following two treatment courses, patients should not be administered additional MAVENCLAD during the next two years. Treatment during these two years may further increase the risk of malignancy. The safety and efficacy of MAVENCLAD more than two years after completing two treatment courses has not been studied.

Dr. Caudle:
Excellent, very helpful, very helpful. Let's move forward. Can you share some examples of eligible MAVENCLAD patients?

Dr. Negroski:
Well, one particular example was a 29-year-old female that developed optic neuritis. She had an incomplete recovery of her optic neuritis. Her MRI was positive. She was diagnosed with multiple sclerosis with strict criteria. She was placed on an injectable drug, and after 2 years unfortunately had another clinical relapse, although it caused motor weakness in her leg. An MRI was carried out for 2 years, and with each MRI she had 3 new lesions. She admitted that she was actually noncompliant with her injectable therapy, largely because of activities and things like that. So she was a candidate for discussion regarding the possible use of another option, MAVENCLAD, for treating her relapsing form of multiple sclerosis. The issue is pregnancy, obviously, but she assured that she would use effective contraception, and she did not have an active malignancy, so we had a conversation that she may be an appropriate candidate for MAVENCLAD.

Dr. Edmonds:
I have a lady who is going to go on Mavenclad. She's 33 years old. She's had MS since she was 15. She was originally on an injectable medication, but because she was so young, she was very noncompliant, and she developed a lot of disability while on that medication. Then she went to an infusible medication—she's been on it for many years—and otherwise, she has no medical contraindications. She has an IUD, so she will not get pregnant. We've screened her for hepatitis B and C, and she has no risk for HIV. She doesn't have... She screened negative for TB. She just had her MRI scan today, and then she'll be ready to get her Mavenclad.

Dr. Caudle:
Yes, absolutely. Well, that's very helpful to sort of provide that clinical example of who might benefit from this drug.

Dr. Caudle:
I want to thank my guests, Dr. Timothy West, Dr. Donald Negroski, Mary Kay Fink and Dr. Elaine Edmonds for helping us better understand MAVENCLAD from a clinical perspective.

For ReachMD, I'm your host, Dr. Jennifer Caudle, and thank you for joining us.

Announcer:
INDICATION

MAVENCLAD® (cladribine) tablets is indicated 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.

Limitations of Use: MAVENCLAD is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile.

IMPORTANT SAFETY INFORMATION

WARNING: MALIGNANCIES and RISK OF TERATOGENICITY

- **Treatment with MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy. In patients with prior malignancy or with increased risk of malignancy, evaluate the benefits and risks of the use of MAVENCLAD on an individual patient basis. Follow standard cancer screening guidelines in patients treated with MAVENCLAD**

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- **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 harm. Malformations and embryolethality 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 dosing and for 6 months after the last dose in each treatment course. Stop MAVENCLAD if the patient becomes pregnant**

CONTRAINDICATIONS

- Patients with current malignancy.
- Pregnant women, and women and men of reproductive potential who do not plan to use effective contraception during and for 6 months after the last dose in each treatment course. May cause fetal harm.
- Patients with human immunodeficiency virus (HIV).
- Patients with active chronic infections (e.g., hepatitis or tuberculosis).
- Patients with a history of hypersensitivity to cladribine.
- Women intending to breastfeed while taking MAVENCLAD tablets and for 10 days after the last dose.

WARNINGS AND PRECAUTIONS

- **Malignancies**: Treatment with MAVENCLAD may increase the risk of malignancy. After the completion of 2 treatment courses, do not administer additional MAVENCLAD treatment during the next 2 years. The risk of malignancy with reinitiating MAVENCLAD more than 2 years after the completion of 2 treatment courses has not been studied. Follow standard cancer screening guidelines in patients treated with MAVENCLAD.
- **Risk of Teratogenicity:** MAVENCLAD may cause fetal harm when administered to pregnant women. In females of reproductive potential, exclude pregnancy before initiation of each treatment course of MAVENCLAD and prevent by the use of effective contraception during MAVENCLAD dosing and for at least 6 months after the last dose of each treatment course. Women who become pregnant during treatment with MAVENCLAD should discontinue treatment.
- **Lymphopenia:** MAVENCLAD causes a dose-dependent reduction in lymphocyte count. In clinical studies, 87% of MAVENCLAD-treated patients experienced lymphopenia. The lowest absolute lymphocyte counts occurred approximately 2 to 3 months after the start of each treatment course and were lower with each additional treatment course. Concomitant use of MAVENCLAD with hematotoxic drugs may increase the risk of adverse reactions because of the additive hematological effects. Monitor lymphocyte counts before and during treatment, periodically thereafter, and when clinically indicated.
- **Infections:** MAVENCLAD can reduce the body's immune defense and may increase the likelihood of infections. Infections occurred in 49% of MAVENCLAD-treated patients compared to 44% of patients treated with placebo in clinical studies. The most frequent serious infections included herpes zoster and pyelonephritis. Single fatal cases of tuberculosis and fulminant hepatitis B were reported in the clinical program. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD. Screen patients for latent infections; consider delaying treatment until infection is fully controlled. Vaccinate patients antibody-negative to varicella zoster virus prior to treatment. Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter. Monitor for infections. In patients treated with parenteral cladribine for oncologic indications, cases of progressive multifocal leukoencephalopathy (PML) have been reported. No case of PML has been reported in clinical studies of cladribine in patients with MS.
- **Hematologic Toxicity:** In addition to lymphopenia, decreases in other blood cells and hematological parameters have been reported with MAVENCLAD in clinical studies. In general, mild to moderate decreases in neutrophil counts, hemoglobin levels, and platelet counts were observed. Severe decreases in neutrophil counts were observed in 3.6% of MAVENCLAD-treated patients, compared to 2.8% of placebo patients. Obtain complete blood count (CBC) with differential including lymphocyte count before and during treatment, periodically thereafter, and when clinically indicated.
- **Risk of Graft-versus-Host Disease With Blood Transfusions:** Transfusion-associated graft-versus-host disease has been observed rarely after transfusion of nonirradiated blood in patients treated with cladribine for non-MS treatment indications.
- **Liver Injury:** In clinical studies, 0.3% of MAVENCLAD-treated patients had liver injury (serious or causing treatment discontinuation) compared to 0 placebo patients. Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to treatment. Discontinue if clinically significant injury is suspected.
- **Hypersensitivity:** In clinical studies, 11% of MAVENCLAD-treated patients had hypersensitivity reactions, compared to 7% of placebo patients. Hypersensitivity reactions that were serious and/or led to discontinuation of MAVENCLAD, occurred in 0.5% of MAVENCLAD-treated patients, compared to 0.1% of placebo patients. If a hypersensitivity reaction is suspected, discontinue MAVENCLAD therapy. Do not use MAVENCLAD in patients with a history of hypersensitivity to cladribine.

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- **Cardiac Failure:** In clinical studies, one MAVENCLAD-treated patient experienced life-threatening acute cardiac failure with myocarditis, which improved after approximately one week. Cases of cardiac failure have also been reported with parenteral cladribine used for treatment indications other than multiple sclerosis.

Adverse Reactions: The most common adverse reactions with an incidence of >20% for MAVENCLAD are upper respiratory tract infection, headache, and lymphopenia.

Drug Interactions/Concomitant Medication: Concomitant use of MAVENCLAD with immunosuppressive or myelosuppressive drugs and some immunomodulatory drugs (e.g., interferon beta) is not recommended and may increase the risk of adverse reactions. Acute short-term therapy with corticosteroids can be administered.
Avoid concomitant use of certain antiviral and antiretroviral drugs. Avoid concomitant use of BCRP or ENT/CNT inhibitors as they may alter bioavailability of MAVENCLAD.

Use in Specific Populations: Studies have not been performed in pediatric or elderly patients, pregnant or breastfeeding women. Use in patients with moderate to severe renal or hepatic impairment is not recommended.

Please see the full Prescribing Information, including boxed WARNING at www.MAVENCLAD.com for additional information.

Announcer:
This program was sponsored by EMD Serono. If you missed any part of this discussion, visit www.ReachMD.com/MSTreatment. This is ReachMD. Be part of the knowledge.

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