Cladribine and Natalizumab

FMEC Responses to Questions From the Drug Programs

Table 1: Response Summary

Drug program implementation questions	Clinical expert response (clinical experts act as guest specialists for FMEC)	FMEC response
Relevant comparators		
The drug programs seek guidance for the unmet need or place in therapy of cladribine and natalizumab amongst the high efficacy drugs for RRMS (e.g., ocrelizumab, ofatumumab, currently reimbursed in first line for RRMS). Are there situations where the use of cladribine or natalizumab may be prioritized over the other treatments and which patient characteristics could help to identify the appropriate patient population? (e.g., natalizumab may be selected for a fast onset of efficacy response for specific patient presentations suggestive of highly aggressive disease — multiple gadolinium-enhancing lesions on MRI, clinical relapses).	The clinical experts commented that cladribine and natalizumab have not been compared in head-to-head trials. The general impression is that natalizumab is a drug with higher efficacy than cladribine. One drug may be favoured over another depending on patient factors, clinical status, comorbidities, age, and preferences. **Natalizumab:** Natalizumab may be preferred in patients with IBD because IBD may be exacerbated by B-cell therapies, such as ocrelizumab or ofatumumab. Natalizumab may also be preferred if a drug with fast onset of action is desired. Natalizumab may be preferred in patients with difficulty adhering to oral therapy or with a history of cancer (and cladribine is contraindicated, although a past history of cancer is not an absolute contraindication). The clinical experts also noted that natalizumab may be appropriate to considering individuals who are at low risk for PML (JCV negative or low JC virus titre). **Cladribine:** Cladribine is another option considered for patients with a contraindication to or heightened precaution for using B-cell therapies (e.g., ocrelizumab, ofatumumab). Cladribine	FMEC defers to the experts.

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	may be preferred in patients who prefer oral therapy, would like to try for pregnancy within 1.5 to 2 years, have difficulty with needles or infusions, or are older and a shorter duration of immunosuppression is desired. Cladribine may also be preferred for individuals with very low or high BMIs because the dose of cladribine can be adjusted based on weight.	
Considerations for initiation of therapy		
The drug programs seek guidance on parameters used to confirm diagnosis or clinical presentation of a patient that would be considered appropriate for first-line treatment with cladribine for funders to apply the criteria in this population (e.g., MRI results, T2 lesions, lesional location, comorbidities such as cancer or infection risk, age, frailty, cognitive impairment, family planning, PML risk, and other relevant factors).	The clinical experts noted that any of the following parameters can be used to confirm diagnosis or clinical presentation of a patient that would be considered appropriate for first-line treatment with cladribine or natalizumab: • a moderate or severe relapse in the past 2 years • a gadolinium-positive lesion on MRI • any history of relapse with poor recovery • high baseline lesion burden on MRI. However, the clinical experts noted that there is no consensus among prescribers and the decision for treatment should be left to the treating MS specialist to allow flexibility over time. Other additional considerations for cladribine include contraindication or heightened precaution regarding receiving B-cell therapy (e.g., ocrelizumab, ofatumumab) and older age. Other additional considerations for natalizumab include having a low risk for PML and contraindication or heightened precaution regarding receiving B-cell therapy (e.g., ocrelizumab, ofatumumab) and younger age.	Please refer to the initiation conditions in the recommendation report.

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The drug programs seek guidance on parameters that could be used to identify the patient characteristics and define population that would most benefit from first-line access to cladribine or natalizumab to help adjudicate requests. In what clinical situations would it be appropriate to avoid using cladribine or natalizumab in the first line?	The clinical experts suggested cladribine should be avoided or require additional considerations in the following situations: • presence of moderate to severe lymphopenia at baseline • immunocompromised state • latent or active infections • history of PML • moderate or severe renal impairment • pregnancy or breast feeding • reproductive potential without effective contraception during dosing and for 6 months after the last dose (male and female) • hereditary fructose intolerance • personal history of cancer may be considered with caution (note: cladribine is contraindicated in patients with active malignancy; in patients with prior malignancy, individual benefit-risk evaluation is required, and history of cancer is not an absolute contraindication) • positive TB test (requires further evaluation for latent TB which should be treated before starting cladribine) The clinical experts suggested natalizumab should be avoided or require additional considerations in the following situations: • any previous concern for PML (according to the most recent evidence, natalizumab should be prescribed with consideration of JCV index, and appropriate risk management strategies for PML) • immunocompromised state • active malignancy • older age (> 55 years) because there is insufficient data regarding its safety in this population	FMEC defers to the experts.

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Are there instances in which it would be reasonable to reinitiate therapy for a patient who may have had suboptimal response to natalizumab or discontinued therapy due to AE?	The clinical experts suggested that it would not be reasonable to reinitiate natalizumab if there has been a suboptimal response. In the case of adverse reactions, reinitiation would depend on the type of adverse reaction.	FMEC defers to the experts.
Considerations for continuation or renewal of therapy		
What is the monitoring requirement for therapeutic response via MRI for all DMTs (not specific to drugs under review)? Is the interval to perform an initial new baseline MRI different between agents? Do subsequent monitoring intervals depend on clinical response? Is there a more frequent monitoring requirement via MRI for patients treated with natalizumab due to risk of PML (and be further dictated by patient-specific factors)?	MRIs are obtained at least annually in the first few years of treatment for all DMTs. More frequent MRIs are required for monitoring for PML and in active MS. One clinical expert suggested a new baseline MRI can be done at 6 months after starting the drug, although it is reasonable to do it earlier (3 months) for natalizumab. For cladribine, some clinicians suggested to perform a new baseline MRI at 2 years, perhaps due to limited resources. Patients with active disease should be switched earlier to another DMT. MRIs should be done at least annually indefinitely as long as the patient is on natalizumab treatment. If a patient has a high JCV index on natalizumab, then the frequency of MRI can vary but should be done every 3 to 6 months.	FMEC defers to the experts.
Considerations for discontinuation of therapy		
What discontinuation criteria could be considered for drugs under review to mitigate any safety concerns for these agents in first line? (e.g., Are there discontinuation criteria that should be considered for natalizumab and when a patient may need to switch to another treatment due to increased PML risk in the older population?)	The clinical experts suggested that these drugs should only be prescribed by neurologists with expertise in MS, who are familiar with their safety concerns. Natalizumab is not recommended for older patients (> 55 years) because there are insufficient data regarding use of natalizumab in this population. It may not be appropriate for patients with high JCV index (> 0.9) to remain on	FMEC defers to the experts.

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	natalizumab for a long period of time (e.g., more than 2 years.) One clinical expert emphasized that natalizumab should be discontinued when the patient has an unacceptable PML risk or has other contraindications.[a] The clinical experts suggested that prescribing physicians should refer to the most recent evidence available on PML risk mitigation.	

AE = adverse event; BMI = body mass index; DMT = disease-modifying therapy; FMEC = Formulary Management Expert Committee; IBD = inflammatory bowel disease; JCV = John Cunningham virus; MRI = magnetic resonance imaging; MS = multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; PML = progressive multifocal leukoencephalopathy; TB = tuberculosis.

[a] Morrow SA, Clift F, Devonshire V, et al. Use of natalizumab in persons with multiple sclerosis: 2022 update. *Multiple Sclerosis and Related Disorders*. 2022;65:103995. doi:10.1016/j.msard.2022.103995