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 1L 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 higher efficacy drug 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 inflammatory bowel disease (IBD) since IBD may be exacerbated by B-cell therapies such as ocrelizumab or ofatumumab. Natalizumab may also be preferred in those with multiple gadolinium enhancing lesions or multiple relapses within a year, where 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 (where cladribine is contraindicated) The clinical experts also noted that natalizumab may be preferred in individuals who are at low risk for PML (JCV negative or low JC virus titre). Cladribine: Cladribine is also considered for patients with contraindication or heightened precaution to using B-cell therapies (e.g., ocrelizumab, ofatumumab). Cladribine may be preferred in patients who prefer oral therapy, in patients would like to try for pregnancy in 1.5-2 years, with difficulty with needles or infusions or older patients for whom a shorter duration of immunosuppression is desired. Cladribine may also be preferred for individuals with very low or high BMIs since dose of cladribine can be adjusted.	FMEC defers to the experts
Considerations for initiation of therapy		

Drug Program Implementation Questions	Clinical expert response (Clinical experts act as guest specialists for FMEC)	FMEC response
The drug programs seek guidance on parameters used to confirm diagnosis or clinical presentation of a patient that would be considered appropriate for 1L 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 the following parameters can be used to confirm diagnosis or clinical presentation of a patient that would be considered appropriate for 1L treatment with cladribine or natalizumab: • A moderate or severe relapse in the past two years OR • Gadolinium positive lesion on MRI OR • Any history of relapse with poor recovery OR • High baseline lesion burden on MRI Other additional considerations for cladribine include contraindication or heightened precaution regarding receiving B cell therapy (e.g. ocrelizumab, ofatumumab) and older patients. 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 patients. When considering patients who may be considered highly active relapsing MS, one clinical expert suggest it may be defined as patient having one relapse in the previous year and at least one T1 gadolinium positive lesion, or 9 or more T2 lesions while on other DMTs, or 2 or more relapses in the previous year, whether on DMT or not. This was how "highly active MS" was defined in literature evaluating cladribine.[1,2]	FMEC defers to the experts. Please refer to the initiation conditions in the recommendation report.

[1] Brochet B, Hupperts R, Langdon D, Solari A, Piehl F, Lechner-Scott J, Montalban X, Selmaj K, Valis M, Rejdak K, Havrdova EK, Patti F, Alexandri N, Nolting A, Keller B. Treatment satisfaction, safety, and tolerability of cladribine tablets in patients with highly active relapsing multiple sclerosis: CLARIFY-MS study 6-month interim analysis. Mult Scler Relat Disord. 2022 Jan;57:103385. doi: 10.1016/j.msard.2021.103385. Epub 2021 Nov 9. PMID: 35158476.

[2] Borriello G, Chisari CG, Maimone D, Mirabella M, Paolicelli D, Assogna F, Caradonna S, Patti F. Cladribine effects on patient-reported outcomes and their clinical and biometric correlates in highly active relapsing multiple sclerosis at first switch: the observational, multicenter, prospective, phase IV CLADFIT-MS study. Front Neurol. 2024 Jul 18;15:1422078. doi: 10.3389/fneur.2024.1422078. PMID: 39114529; PMCID: PMC11305121.

Drug Program Implementation Questions	Clinical expert response (Clinical experts act as guest specialists for FMEC)	FMEC response
The drug programs seek guidance on parameters that could be used to identify the patient characteristics and define population that would most benefit from 1L 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 suggest the following situations should avoid cladribine or require additional considerations: • Moderate to severe lymphopenia at baseline • Immunocompromised • Latent or active infections • History of PML • Moderate or severe renal impairment • Pregnant or breast feeding • Patients with reproductive potential not using effective contraception during dosing and for 6 months after last dose (male and female) • Hereditary fructose intolerance • Personal history of cancer may be considered with caution. 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. • A positive TB test requires further evaluation for latent TB which should be treated prior to starting cladribine. The clinical experts suggest the following situations should avoid natalizumab or require additional considerations: • Any previous concern for PML (note that patients positive for JCV with titre >0.9 may receive natalizumab for a short-term period e.g., 1 year; it is considered by one clinical expert acceptable to treat patients with low positive titres for longer durations) • Immunocompromised • Active malignancy • Other patients (> 55) due to insufficient data regarding its safety in the population	FMEC defers to the experts
Are there instances in which it would be reasonable to re-initiate therapy for a patient who may have had suboptimal response to natalizumab or discontinued therapy due to AE?	The clinical experts suggest that it would not be reasonable to reinitiate natalizumab if there has been a suboptimal response. In the case of adverse reactions, re-initiation would depend on the type of adverse reaction.	FMEC defers to the experts
Considerations for continuation or renewal of therapy		

Drug Program Implementation Questions	Clinical expert response (Clinical experts act as guest specialists for FMEC)	FMEC response
What is the monitoring requirement for therapeutic response via MRI for all DMTs (not specific to drugs under review)? Is the interval for initial re-baseline different between agents? Do subsequent monitoring intervals depend on clinical response? Is there more frequent monitoring requirement via MRI for natalizumab-treated patients 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 suggests re-baseline MRIs can be done at 6 months after drug start or reasonable to do earlier (3 months) for natalizumab. For cladribine, some clinicians would argue to re-baseline MRI at 2 years. Patients with active disease should be switched earlier. MRI should be done at least annually indefinitely as long as patient is on natalizumab. If a patient has a high JCV index on natalizumab, then MRI should be done every 6 months.	FMEC defers to the experts
Currently, the product monograph for cladribine supports the use of two treatment courses, with a potential to delay the second treatment course in the second year by up to 6 months. What treatment would be used in clinical practice to manage a relapse/clinical attack occurring after the second treatment course of cladribine?	The clinical experts indicate that if a relapse occurs after two cycles of cladribine, there is evidence to support a third cycle of cladribine can offer greater efficacy. This is a practice that has been adopted by many neurologists globally. Another approach would be to switch to a B-cell therapy (e.g., ocrelizumab or ofatumumab). Other high efficacy DMTs are also potential treatment options, such as fingolimod, natalizumab or alemtuzumab. The treatment choice should be guided by the individual patient's situation, including the magnitude of responses to cladribine and / or potential contraindications to other options.	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 1L? (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 older population?)	The clinical experts suggest 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), as there are insufficient data regarding use of natalizumab in this population. Patients with high JCV index ≥ 0.9 may not be suitable to remain on natalizumab for a long period of time (e.g., more than 2 years.) One clinical expert emphasizes that natalizumab should be discontinued when the patient has	FMEC defers to the experts.

Drug Program Implementation Questions	Clinical expert response (Clinical experts act as guest specialists for FMEC)	FMEC response
	unacceptable PML risk or other contraindications.[3]	

1L = first line; AE = adverse event; BMI = body mass index; DMT = disease-modifying therapies; 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

[3] Use of natalizumab in persons with multiple sclerosis: 2022 update - Multiple Sclerosis and Related Disorders