

Two newly funded medicines for Chronic Obstructive Pulmonary Disease (COPD)

Recommended treatments for COPD include long-acting muscarinic antagonists (LAMA), such as tiotropium, which act on a subtype of cholinergic receptor, and long-acting beta agonists (LABA) such as salmeterol and formoterol fumarate. As of 1 November, 2014, two additional medicines in these classes are now fully subsidised: glycopyrronium, a LAMA, and indacaterol, a LABA. This offers a wider range of treatment options for patients with COPD. Glycopyrronium subsidy is subject to Special Authority approval, with a number of restrictions. Indacaterol is subsidised without restriction.

The exact prevalence of COPD in New Zealand is unknown, but it has been estimated to affect approximately 14% of people aged 40 years and older.¹ Smoking is the main risk factor.² Primary care clinicians have an important role in identifying patients at risk of COPD, diagnosing COPD, referring patients to respiratory specialists and providing ongoing management.

Long-acting muscarinic antagonist (LAMA) or beta-agonist (LABA) inhalations are the recommended first-line treatment for many patients with COPD.³ These include formoterol (also known as eformoterol), tiotropium and salmeterol, which were already fully or partly subsidised, and the newly subsidised glycopyrronium and indacaterol. Other treatment options include short-acting medicines such as salbutamol (a short-acting beta-agonist) and ipratropium bromide (a short-acting muscarinic antagonist), both of which are fully subsidised.

COPD is a progressive condition and stopping smoking in those patients who still smoke is one of the main interventions to improve survival, particularly as many patients will die of cardiac disease rather than respiratory complications.^{2,4}

Access and funding criteria

Glycopyrronium

Glycopyrronium is fully subsidised, subject to Special Authority approval. Initial applications and renewals can be applied for by general practitioners, and both are valid for two years.

A number of restrictions for the initiation of glycopyrronium are in place, including that the patient must have:

- Previously trialled ipratropium bromide for one month
- Grade 4 or 5 breathlessness according to the Medical Research Council (UK) dyspnoea scale*
- A FEV₁ of below 60% of predicted FEV₁

* Grade 4 breathlessness under the MRC dyspnoea scale means stopping for breath after about 100 metres or after walking for a few minutes on the level, and Grade 5 means being too breathless to leave the house, or breathless when dressing or undressing.⁵

Patients should also not be smokers, or alternatively have been offered smoking cessation advice, and they must have been offered an up-to-date influenza vaccination. The same Special Authority criteria apply to tiotropium, and patients can be switched between these two medicines without the need to reapply for Special Authority. However, funding is only for one of these medicines at a time and tiotropium and glycopyrronium should not be used together.

For renewal of Special Authority applications, patients must be compliant with medicine use and show benefit from glycopyrronium.

Indacaterol

Indacaterol is available, fully subsidised, without the need for Special Authority approval.

How do these medicines work?

Glycopyrronium is an inhaled long-acting muscarinic receptor antagonist (LAMA), which acts as a bronchodilator and is indicated for use in patients with COPD. Glycopyrronium is administered as a 50 microgram dose, once daily, via inhalation of dry powder using the inhaler device; each dose (supplied as a blister-packed capsule) must be loaded into the inhaler device immediately before use. Patients will need to be instructed on how to use the inhaler. It is designed to give feedback when a dose is taken correctly, with an audible whirring noise after dose delivery, and patients are able to check that the delivery capsule is empty. It is rapidly absorbed and reaches peak plasma levels five minutes after administration. Based on data from clinical trials, the expected benefit is likely to be in the range of a 100 mL increase in forced expiratory volume (FEV₁).⁶ The result for patients therefore is an improvement in breathlessness and exercise tolerance.

Indacaterol is a long-acting beta-agonist (LABA) for the treatment of patients with COPD. It is taken by inhalation as a once daily dose of 150 micrograms or 300 micrograms. Indacaterol is also administered by loading a capsule containing the dry powder dose into the inhaler device, and patients will need to be instructed in its use. Meta-analyses of trials including patients taking indacaterol for the treatment of COPD report that patients experience an improvement in respiratory symptoms to a similar or slightly greater extent than with other bronchodilators such as tiotropium, salmeterol or formoterol.^{7,8} Overall efficacy in terms of improvements in FEV₁ scores appears similar to treatment with these comparator medicines.^{7,8} For patients with stable COPD, maximal benefit is likely to be gained at a 150 microgram, once daily, dose.⁷


Adverse effects

The most frequently reported adverse effect of glycopyrronium is dry mouth, related to its antimuscarinic action. Other adverse effects include dyspepsia and gastroenteritis, insomnia, irritation affecting the nasal and throat passages, rhinitis and sinusitis.^{9,10} Given its anticholinergic effects, glycopyrronium should be used with caution in patients with narrow-angle glaucoma or urinary retention, as well as in patients with renal impairment.¹⁰ The European Medicines Authority has recommended that post-marketing studies include more detailed assessments of possible cardiovascular adverse effects, after higher rates of atrial fibrillation were observed in one clinical trial.^{6,9}

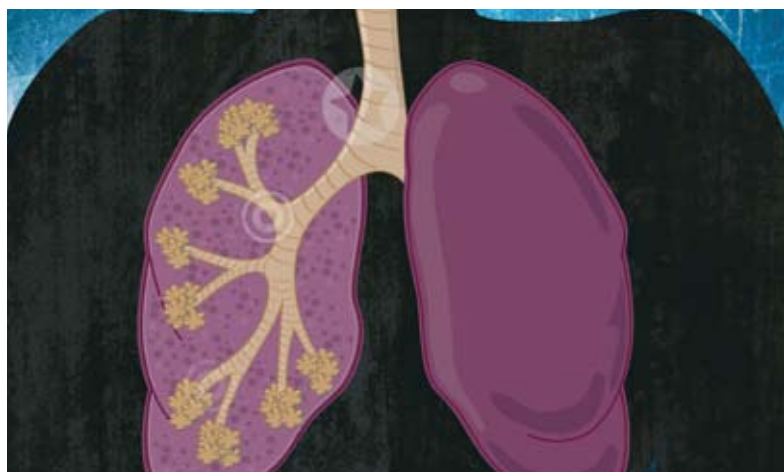
Adverse effects of indacaterol include nasopharyngitis and headache, insomnia, tachycardia and muscle cramps.^{7,8,11,12} Indacaterol does not protect against exacerbations of COPD, nor worsening of symptoms.⁸ Beta-agonists may cause potential systemic effects such as tachycardia, and should be used with caution in patients with cardiovascular disease, or thyrotoxicosis where tachycardia is already present and the patient has possible increased sensitivity to beta agonists.¹³

Combination treatment

A combination indacaterol/glycopyrronium inhaled powder has been investigated for effectiveness in the treatment of patients with COPD and shows some benefit over either treatment alone.^{14,15} It is possible that this preparation may also be subsidised on the Pharmaceutical Schedule in the future.

 For further information on managing patients with COPD, see: www.bpac.org.nz/BPJ/2012/April/copd.aspx

N.B. An update on COPD management is planned for Best Practice Journal in 2015.

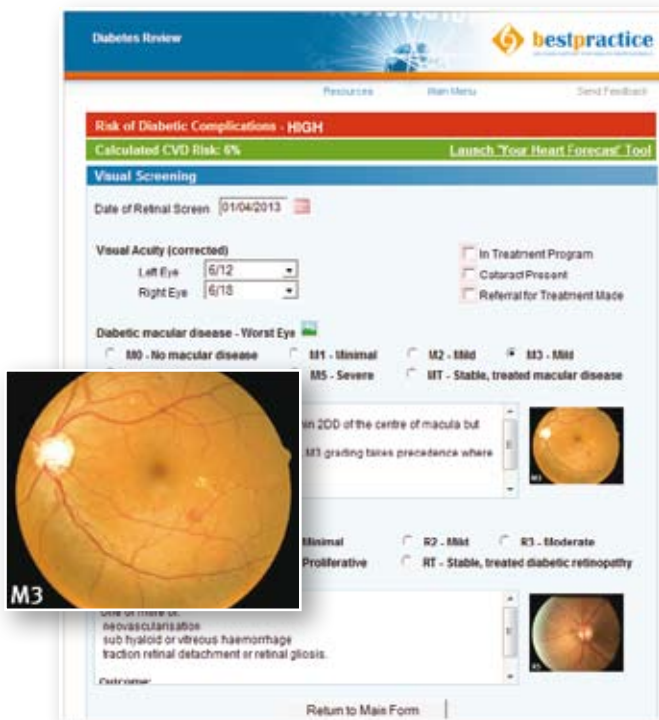




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Rivastigmine patches (Exelon) now funded for patients with dementia

On 1 November, 2014, rivastigmine patches were newly funded on the national Pharmaceutical Schedule for the management of patients with dementia. Two strengths of patches are now funded as a second-line treatment for dementia, subject to Special Authority criteria. Patients first must have tried oral donepezil but have experienced intolerable nausea and vomiting. Rivastigmine is equally effective as donepezil.

Approximately 30,000 people in New Zealand are estimated to be living with Alzheimer's disease,¹ the primary cause of dementia, and general practitioners are often the first point of contact for patients or their family members who may have concerns over memory problems or behaviour changes.

International guidelines recommend that initial evaluations for the diagnosis of dementia include an assessment of patient history, with information from family members and people familiar with the patient, as well as some form of cognitive test, such as the Mini Mental State Examination.^{2,3} Investigations such as complete blood count, renal and liver function tests, thyroid-stimulating hormone, electrolytes, calcium, glucose, folate and vitamin B12 levels may be considered, as these can help to exclude other differential diagnoses or additional causes of cognitive impairment.^{2,3} Patients with suspected dementia are likely to require referral to a geriatrician or psychiatrist to confirm a diagnosis as other tests and imaging may be required.

There are no medicines or lifestyle interventions which have been shown to reverse or cure dementia. As dementia influences many aspects of a person's daily life, and in turn

the lives of those around them, care of patients with dementia and their families revolves around the provision of support services, including counselling to promote independence in activities of daily living and to provide psychological support.³ Medicines indicated for the treatment of dementia are not a cure, and act only to improve or delay symptoms. In New Zealand, the acetylcholinesterase inhibitor donepezil, taken orally, is fully funded as a first-line treatment for dementia. Rivastigmine patches are a second-line treatment if donepezil tablets are not tolerated. Galantamine and memantine are also indicated for the management of dementia in patients with Alzheimer's disease, but are not subsidised.

Access and subsidy criteria for rivastigmine patches

The approved indication for rivastigmine is for the management of patients with dementia due to Alzheimer's disease. Its use in patients with dementia due to other causes such as Parkinson's disease or Lewy body dementia is an unapproved indication, however, these patients may benefit from rivastigmine treatment,⁴ and the Special Authority criteria do not limit access to specific causes of dementia.

Rivastigmine patches at two strengths, 4.6 mg/24 hours (5 cm² patch) and 9.5 mg/24 hours (10 cm² patch), are fully subsidised subject to Special Authority criteria for use in patients intolerant to the gastrointestinal side effects of donepezil. Applicants will need to confirm the patient has dementia and has experienced intolerable nausea and/or vomiting from donepezil tablets, which is estimated to occur in approximately 15% of patients.⁴ Initial applications are valid for six months and renewal applications can be made if the patient shows benefit, and are valid for another 12 months.

How does rivastigmine work?

The biological processes that lead to dementia in Alzheimer's disease are not entirely understood, but alterations are seen in key synaptic pathways using the neurotransmitter acetylcholine.⁵ Medicines which increase acetylcholine levels have been shown to improve cognitive performance in patients with dementia.⁶⁻⁸ Rivastigmine is a cholinesterase inhibitor that blocks the enzymes involved in acetylcholine degradation, and primarily acts in the central nervous system.⁹ Clinical trials of rivastigmine have reported that in patients with dementia it can improve assessments of cognitive function compared with placebo, as well as improvements in daily living activities.⁷ Data from clinical trials show that cognitive measures improve gradually over the course of months.⁷ Caregivers report a preference for rivastigmine patches rather than oral tablets in countries where both oral rivastigmine and patches have been available, due to factors such as ease of use and low interference with daily living.^{10,11}

How are rivastigmine patches given?

Rivastigmine patches are applied to the skin once daily, and should be removed and changed for a new patch after 24 hours. Because of the potential for skin site reactions, patches should be reapplied to a different area of skin, although this may be in the same anatomical region (e.g. back), avoiding the same area for the following 14 days. Patches may be worn during everyday activities such as bathing, but prolonged exposure to external heat sources should be avoided, e.g. direct sun or heaters.

Dosing should begin with the smaller 5 cm² patch, which delivers 4.6 mg over 24 hours, and increase to the larger 10 cm² (9.5 mg/24 hour) patch after four weeks if the lower dose was tolerated.¹² The higher dose patch is regarded as the target

dose, with the lower dose patch used for titration.⁴ If patients have previously been taking oral donepezil, those taking 5 mg orally per day may be switched to the lower dose transdermal patch (4.6 mg) and those usually taking 10 mg orally per day and tolerating this dose may be switched to a 9.5 mg patch.¹³


Adverse effects are to be expected but are usually not serious

The majority of patients taking rivastigmine experience adverse effects; most often these are application site reactions, but also include gastrointestinal symptoms such as nausea, vomiting and diarrhoea, as well as anorexia, headache, syncope, dizziness, falls and extrapyramidal symptoms.^{7, 13, 14} Serious adverse effects are rare.^{7,14} Patients taking rivastigmine via transdermal patches show lower rates of gastrointestinal adverse effects than those taking rivastigmine capsules,¹⁴ and therefore patients who have experienced gastrointestinal adverse effects while taking donepezil may find transdermal rivastigmine more tolerable.

Rivastigmine should be used cautiously in patients with hepatic impairment, as this may reduce drug clearance and result in more adverse effects; adverse effects may also be more prevalent in patients weighing less than 50 kg. As rivastigmine can have cholinergic effects, it should also be used cautiously in patients at risk of urinary obstruction, gastric ulceration or seizures, with COPD or asthma or with defects of cardiac conduction.¹²

In all patients, rivastigmine treatment should be stopped if gastrointestinal adverse effects occur or there are extrapyramidal effects, but treatment can continue once these resolve.¹² If symptoms reappear, it may be necessary to reduce the dose.

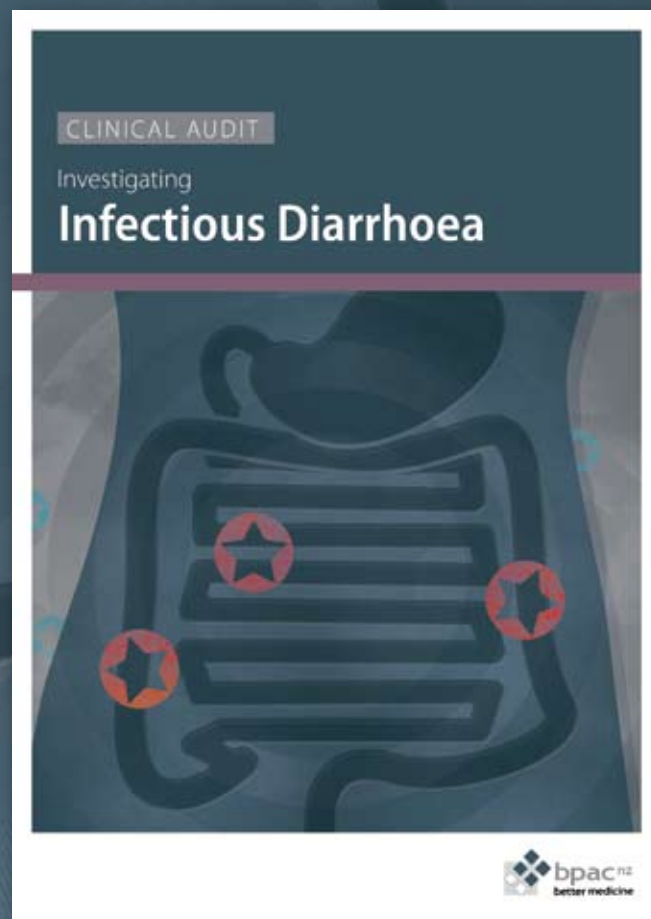
Adverse effects are more likely to occur if a carer or the patient does not remove the previous patch prior to applying another.¹² Practical reminders may be helpful such as a note placed on the medicine box, or establishing a routine of always throwing out the discarded pouch from the new patch with the previous day's removed patch inside it.

 For further information of the use of donepezil in patients with Alzheimer's disease, see: www.bpac.org.nz/BPJ/2010/August/alzheimers.aspx

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Access to medicines for people with multiple sclerosis has changed

From 1 November 2014, people diagnosed with relapsing-remitting multiple sclerosis (MS) were able to be initiated on two new fully-subsidised, disease-modifying medicines, at an earlier stage in the disease process. These medicines are:

- Fingolimod capsules – initiated in secondary care (see below) and dispensed from community pharmacies
- Natalizumab intravenous infusions – administered in secondary care

Fingolimod and natalizumab are now effectively the first-line treatments for people with relapsing-remitting MS. The “ABC medicines” – interferon beta-1a (Avonex), interferon beta-1b (Betaferon) and glatiramer acetate (Copaxone) – will still be fully subsidised, but only as second-line treatments if fingolimod and natalizumab are not tolerated, or are not clinically appropriate. However, the “ABC” medicines will continue to be subsidised for people who were receiving one of these treatments prior to 1 November 2014; therefore these people do not need to switch treatment unless they wish to.

People with multiple sclerosis now have earlier access to treatment


The entry criteria that people must meet to receive fully-subsidised treatment for relapsing-remitting MS has been changed. Natalizumab and fingolimod can now be initiated earlier in the disease process and there is no longer a need for the person to experience frequent relapses before qualifying

for subsidised treatment. Fingolimod and natalizumab are now subsidised:

- From the first confirmed diagnosis of definitive relapsing-remitting MS for people with an Expanded Disability Status Scale (EDSS)* score of 0 – 4.0 who meet the subsidy criteria
- For people with MS with one significant relapse in the previous 12 months, or two significant relapses in the previous 24 months. Treatment can be initiated once the diagnosis of MS has been confirmed. Previously, people with MS had to display frequent relapses and significant residual disability to qualify for subsidised treatment.


* The Kurtzke EDSS is a method of quantifying disability in patients with MS. The assessment is undertaken in secondary care and is used to measure and assess disability and disease progression in patients with MS.

General practitioners are encouraged to review the treatment of all patients with an existing diagnosis of MS who potentially meet the new funding criteria. It is important that general practitioners refer patients with symptoms suggestive of MS early to a neurologist for assessment. Earlier access to disease-modifying medicines may slow progression of MS and result in reduced disability for some people (see below).

 Specific details about eligibility criteria for MS treatments, and other information, can be found in the Questions and Answers on the PHARMAC MS treatments webpage at: www.pharmac.health.nz/news/notification-2014-10-10-mstreatments/

Relapsing-remitting multiple sclerosis

A relapsing-remitting pattern of disease is seen in 85% of people with early stage MS.¹ This is characterised by recurrent acute neurological episodes, with residual symptoms increasing or new symptoms developing. On average, people with MS have approximately one relapse every two years, however, the frequency and severity of these can vary widely.² A high frequency of relapses during the first two years of the disease increases the risk that the person with MS will progress to secondary progressive MS and long-term disability.²

 For further information, see: "Multiple sclerosis: Managing shades of grey", BPJ 54 (Aug, 2013).

General practitioners may be required to prescribe fingolimod

General practitioners may be requested to provide repeat prescriptions for fingolimod following approval of the initial treatment application by the Multiple Sclerosis Treatment Advisory Committee (MSTAC). Fingolimod is available in 500 microgram capsules, which are taken once daily.

Compared with the injectable "ABC" MS treatments, fingolimod has a wider-ranging immunosuppressant action.³ It inhibits leukocyte migration across the blood-brain barrier and therefore reduces inflammation in the central nervous system.⁴ This occurs through an agonist action at sphingosine-1-phosphate receptors.³ A two-year trial reported that, in comparison to placebo, fingolimod more than halved the rate of relapse in people with relapsing-remitting MS.³ A possible decrease in disease progression was also noted.³ Compared with once-weekly subcutaneous injections of interferon beta-1b, fingolimod is reported to reduce the annual rate of relapse in people with relapsing-remitting MS.³

Fingolimod is contraindicated in people who are undergoing immunosuppressant treatment, have active infection or an active malignancy (other than basal cell carcinoma).⁵ Fingolimod is not recommended for people with an increased cardiovascular risk as it may cause bradycardia and heart block due to its effects on the sphingosine-1-phosphate receptors on the heart.⁵ Fingolimod may also not be appropriate for people with other cardiac conditions (see NZF for more details).

Discussion with a cardiologist is strongly recommended prior to starting fingolimod in a patient with a history of cardiovascular issues. The clinician managing the patient's treatment for MS should be informed if the patient develops any clinically significant cardiovascular symptoms while taking fingolimod.

Patients will require intensive cardiac monitoring in a secondary care setting the first time they take fingolimod. All patients should have an ECG performed prior to dosing and continuously for the first six hours after treatment initiation.^{5,6} If any cardiac effects are observed, extended monitoring (at least overnight) will be required.⁵ Hourly blood pressure and heart rate measurements should also be taken for the first six hours of treatment.^{5,6}

It is recommended that people who do not have a validated history of varicella or a documented full course of varicella vaccine undergo varicella zoster antibody testing prior to starting fingolimod.⁵ A full course of varicella vaccine should be administered in patients who are varicella antibody-negative and the initiation of fingolimod treatment delayed for one month to allow the vaccine to reach full effectiveness.

Other adverse effects associated with fingolimod include: diarrhoea, weight loss, abnormal liver function tests, hypertension, cough, dyspnoea, depression, malaise, headache, dizziness, paraesthesia, influenza, bronchitis, sinusitis, gastroenteritis, tinea infections, back pain, asthenia, blurred vision, eye pain, eczema, alopecia and pruritus.⁵ As expected with an immunosuppressive treatment, people taking fingolimod have an increased risk of infectious complications, particularly due to herpes zoster, skin cancer and other neoplasms.³ Due to the increased risk of macular oedema, patients should undergo an ophthalmic examination before beginning treatment and regularly thereafter.³ Pregnancy is an absolute contraindication to the use of fingolimod and should be excluded.³ Effective contraception should be used until at least two months after treatment has finished.³


Natalizumab infusions are administered in secondary care

Natalizumab is an intravenous infusion, given every four weeks in secondary care for the treatment of people with relapsing-remitting MS. It is available as a 300 mg/15 mL formulation. General practitioners are unlikely to be involved in prescribing natalizumab, but will be involved in monitoring patients for adverse effects. Community pharmacists are unlikely to dispense natalizumab directly to the patient as this will generally be arranged by the hospital pharmacy.

Progressive multifocal leucoencephalopathy (PML)

PML is a rare, and usually fatal, viral disease characterised by progressive damage or inflammation of the white matter of the brain at multiple locations. PML occurs almost exclusively in people with a severe immune deficiency. It is caused by the John Cunningham (JC) virus and is characterised by muscle weakness, sensory deficit, cognitive dysfunction, language impairment – and coordination and gait difficulties. The risk of a patient with MS having PML is approximately 1% if they have a detectable titre for JC virus.³ This risk may be increased in patients who have previously used immunosuppressant medicines.³ The risk of PML is an order of magnitude lower in patients without a detectable titre for JC virus.³

People taking natalizumab also have an increased risk of PML, which increases after two years of treatment.⁵ A MRI scan is recommended before starting natalizumab treatment and annually thereafter. Patients taking natalizumab should be monitored for symptoms of PML. If PML is suspected, natalizumab should be permanently discontinued.⁵

 For further information on PML see: www.medsafe.govt.nz/profs/PUArticles/PMLSept2012.htm



Health professionals who are involved in the prescribing or dispensing of natalizumab will be required to undergo training provided by the manufacturer (the Tysabri Australasian Prescribing Programme). This is due to the potential for patients to develop progressive multifocal leucoencephalopathy (PML), which has a 20% fatality rate in people with MS (see opposite).³

Natalizumab may be the most effective medicine available for treating relapsing-remitting MS.³ It is a humanised monoclonal antibody that blocks receptors on the surface of phagocytic mononuclear cells, preventing them from migrating from peripheral circulation into the central nervous system.³ A review of three studies, one placebo-controlled study (942 patients) and two studies involving adjunctive treatment with either glatiramer acetate (110 patients) or interferon beta-1b (1171 patients), found robust evidence of a reduction in relapses and disability in patients with MS after two years.⁴ It is important that general practitioners discuss any concerns they have about the effectiveness of MS treatments that a patient is taking with the clinician managing the patient's treatment for MS, as patients that are not responding to other medicines may be eligible for treatment with natalizumab.

Natalizumab is contraindicated in: people with PML or active infection, people who are concurrently taking interferon beta-1b or glatiramer acetate, people who are immunosuppressed, or people who have active malignancies other than basal cell carcinoma.⁵

Patients may experience infusion-related adverse effects following administration of natalizumab, e.g. nausea, vomiting, headaches, dizziness, fatigue, fever, or hypersensitivity reactions including anaphylaxis.⁵ Patients should be monitored for these symptoms during the infusion and for one hour after.⁵

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