Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Gelomyrtol; ***Ger.:*** Gelomyrtol; ***Gr.:*** Gelomyrtol; ***Hong Kong:*** Gelomyrtol; ***Neth.:*** Gelodurat; ***Thai.:*** Gelomyrtol.

Multi-ingredient: ***Austria:*** Tetra-Gelomyrtol; ***Braz.:*** Broncopinol†; ***Fr.:*** Acarcid†; Nazinette du Docteur Gilbert; Pectoderme†; ***Ger.:*** Tetra-Gelomyrtol; ***Spain:*** Trophires†.

Nadide *(BAN, USAN, rINN)*

Codehydrogenase I; Coenzyme I; Co-I; Diphosphopyridine Nucleotide; DPN; NAD; Nadida; Nadidum; Nicotinamide Adenine Dinucleotide; NSC-20272. 1-(3-Carbamoylpyridinio)-β-D-ribofuranoside 5-(adenosine-5′-pyrophosphate).

Надид

$C_{21}H_{27}N_7O_{14}P_2$ = 663.4.
CAS — 53-84-9.

Profile
Nadide is a naturally occurring coenzyme claimed to be of value in the treatment of alcohol and opioid addiction. The reduced form of nadide, NADH, has been used in the management of chronic fatigue syndrome.

Parkinsonism. The reduced form of nadide, NADH (β-NADH; reduced DPN) and its phosphate derivative (NADPH) have been given in the management of Parkinson's disease in an attempt to enhance endogenous dopamine synthesis by stimulating the enzyme tyrosine hydroxylase. Although some beneficial effects have been reported in several case series, a placebo-controlled study failed to find any evidence of efficacy and the routine use of NADH has not been recommended.[1]

1. Swerdlow RH. Is NADH effective in the treatment of Parkinson's disease? *Drugs Aging* 1998; **13:** 263–8.

Preparations

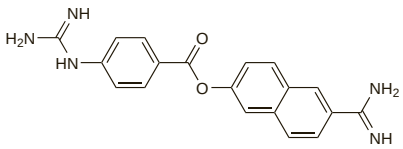
Proprietary Preparations (details are given in Part 3)
S.Afr.: DPN; ***Spain:*** Nad.

Nafamostat Mesilate *(rINNM)*

FUT-175; Mesilato de nafamostat; Nafamostat, Mésilate de; Nafamostat Mesylate *(USAN)*; Nafamostati Mesilas. 6-Amidino-2-naphthyl *p*-guanidinobenzoate dimethanesulfonate.

Нафамостата Мезилат

$C_{21}H_{25}N_5O_8S_2$ = 539.6.
CAS — 81525-10-2 (nafamostat); 82956-11-4 (nafamostat mesilate).



(nafamostat)

Profile
Like aprotinin (p.1055) nafamostat is a proteolytic enzyme inhibitor. The mesilate is used in the treatment of acute pancreatitis and disseminated intravascular coagulation, and as an anticoagulant in haemodialysis.

Hyperkalaemia has been reported.

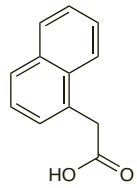
◊ References.

1. Yanamoto H, *et al.* Therapeutic trial of cerebral vasospasm with the serine protease inhibitor, FUT-175, administered in the acute stage after subarachnoid hemorrhage. *Neurosurgery* 1992; **30:** 358–63.
2. Akizawa T, *et al.* Nafamostat mesilate: a regional anticoagulant for haemodialysis in patients at high risk for bleeding. *Nephron* 1993; **64:** 376–81.
3. Miyata T, *et al.* Effectiveness of nafamostat mesilate on glomerulonephritis in immune-complex diseases. *Lancet* 1993; **341:** 1353.
4. Murase M, *et al.* Nafamostat mesilate reduces blood loss during open heart surgery. *Circulation* 1993; **88:** 432–6.
5. Kitagawa H, *et al.* Hyperkalaemia due to nafamostat mesylate. *N Engl J Med* 1995; **332:** 687.
6. Yamazato M, *et al.* Severe abdominal pain associated with allergic reaction to nafamostat mesilate in a chronic hemodialysis patient. *Intern Med* 2002; **41:** 864–6.
7. Kaminishi Y, *et al.* Effects of nafamostat mesilate and minimal-dose aprotinin on blood-foreign surface interactions in cardiopulmonary bypass. *Ann Thorac Surg* 2004; **77:** 644–50.
8. Ota T, *et al.* Cardiopulmonary bypass using nafamostat mesilate for patients with infective endocarditis and recent intracranial hemorrhage. *Interact Cardiovasc Thorac Surg* 2007; **6:** 270–3.

Naphthylacetic Acid

Naftilacético, ácido; 1-Naphthaleneacetic Acid; 1-Naphthylacetic Acid.

$C_{12}H_{10}O_2$ = 186.2.
CAS — 86-87-3.



Profile
Naphthylacetic acid has been used as a choleretic.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Galle-Donau; Spagall; ***Switz.:*** Bilipax†.

Natalizumab *(rINN)*

Natalizumabum. Immunoglobulin G 4 (human-mouse monoclonal AN100226 4-chain antihuman integrin 4), disulfide with human-mouse monoclonal AN100226 light chain, dimer.

Натализумаб

CAS — 189261-10-7.
ATC — L04AA23.
ATC Vet — QL04AA23.

Adverse Effects and Precautions
Natalizumab commonly causes infusion-related reactions including headache, dizziness, fatigue, urticaria, pruritus, rash, fever, rigors, nausea, hypotension, flushing, dyspnoea, and chest pain. Serious hypersensitivity reactions such as anaphylaxis can also occur. These reactions are usually associated with antibodies to natalizumab. The presence of these antibodies results in reduced serum concentrations and efficacy of natalizumab. The risk of infection is increased and there have been a few cases of progressive multifocal leukoencephalopathy (PML) reported; all patients should be monitored and if signs or symptoms of PML appear treatment should be withheld pending investigation. Clinically significant hepatotoxicity has also been reported with natalizumab and treatment should be stopped if there is evidence of jaundice or other significant liver injury.

Natalizumab is contra-indicated in patients who have previously had PML. It is also contra-indicated in patients with, or at risk for, opportunistic infections, and in those with malignancies.

Antibody formation. The incidence and clinical effects of antibody formation to natalizumab therapy in patients with relapsing multiple sclerosis were studied in the AFFIRM and SENTINEL studies.[1] Of 625 patients treated with natalizumab in the AFFIRM study 20 (3%) were transiently positive for antibodies to natalizumab and 37 (6%) were persistently positive. Equivalent figures for 585 natalizumab-treated patients in the SENTINEL study were 32 (5%) and 38 (6%) respectively. Overall the presence of antibodies was generally correlated with reduced serum concentrations of natalizumab and a poorer treatment response, efficacy being restored in those patients who became antibody-negative during therapy. Antibody-positive patients also had a higher incidence of infusion-related adverse effects, including hypersensitivity reactions (17 of the 37 persistently positive patients in the AFFIRM study). It is recommended that patients with suboptimal response to natalizumab or persistent infusion-related adverse effects should be considered for antibody testing. UK licensed product information warns that therapy should not be restarted in patients who remain positive for antibodies 6 weeks after interrupting an initial short exposure to natalizumab.

1. Calabresi PA, *et al.* The incidence and significance of anti-natalizumab antibodies: results from AFFIRM and SENTINEL. *Neurology* 2007; **69:** 1391–1403.

Hypersensitivity. A review[1] of the data for patients who had hypersensitivity reactions in the AFFIRM study[2], which included 627 patients in the natalizumab treatment group, found that there was a low incidence (<1%) of serious reactions described as anaphylactoid or anaphylactic. All patients with hypersensitivity reactions responded promptly to discontinuation of the infusion and standard pharmacotherapy as necessary (adrenaline, oxygen, and antihistamines with or without corticosteroids); all recovered fully about 1 to 2 hours after the end of the infusion. UK licensed product information warns that patients should be counselled on the importance of uninterrupted dosing, particularly in the early months of treatment; the risk for hypersensitivity reactions is greatest with early infusions and in patients who, after an initial short exposure to natalizumab, are re-exposed after a treatment-free period of 3 or more months.

1. Phillips JT, *et al.* Infusion-related hypersensitivity reactions during natalizumab treatment. *Neurology* 2006; **67:** 1717–18. Correction. *ibid.* 2007; **68:** 473.
2. Polman CH, *et al.* AFFIRM investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006; **354:** 899–910.

Infections. Three cases of progressive multifocal leukoencephalopathy (an opportunistic infection of the brain caused by JC virus, a human polyomavirus) have been described in patients given natalizumab.[1-3] One patient[1] died after receiving natalizumab with azathioprine for Crohn's disease. The other patients[2,3] were given natalizumab with interferon beta for multiple sclerosis; one of these[2] also died. After these reports, the use of natalizumab has been restricted (see Uses and Administration, below). A subsequent retrospective evaluation[4] of more than 3000 patients who had received natalizumab found no further cases. However, 2 further cases have subsequently been reported[5] in patients taking natalizumab as monotherapy for 14 months and 17 months; one of the patients had previously taken immunosuppressants.

1. Van Assche G, *et al.* Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *N Engl J Med* 2005; **353:** 362–8.
2. Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. *N Engl J Med* 2005; **353:** 369–74.
3. Langer-Gould A, *et al.* Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. *N Engl J Med* 2005; **353:** 375–81.
4. Yousry TA, *et al.* Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *N Engl J Med* 2006; **354:** 924–33.
5. FDA. Alert for healthcare professionals: natalizumab injection for intravenous use (marketed as Tysabri) (issued 25/08/08). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/natalizumab2008HCP.htm (accessed 26/08/08)

Melanoma. Long-standing naevi in two women developed into melanoma shortly after starting natalizumab treatment for multiple sclerosis.[1]

1. Mullen JT, *et al.* Melanoma complicating treatment with natalizumab for multiple sclerosis. *N Engl J Med* 2008; **358:** 647–8.

Interactions
Use with antineoplastics, immunosuppressants, or immunomodulators may further increase the risk of opportunistic infections including progressive multifocal leukoencephalopathy associated with natalizumab. Concurrent treatment with interferon beta or glatiramer acetate is contra-indicated.

Uses and Administration
Natalizumab is a murine monoclonal antibody raised against human α4 integrin that is used as monotherapy to prevent relapses and delay progression of disability in patients with highly active relapsing-remitting multiple sclerosis. It is also used for inducing and maintaining response and remission in moderate to severe Crohn's disease (see Inflammatory Bowel Disease, p.1697). However, because of an increased risk of progressive multifocal leukoencephalopathy (PML) its availability is restricted, and use is limited to patients who have had an inadequate response to, or are unable to tolerate, other therapies. A baseline magnetic resonance imaging scan must be done before natalizumab is started in order to differentiate newly developed lesions from pre-existing lesions. Patients should be evaluated for signs and symptoms of PML at 3 and 6 months after the first dose, then every 6 months thereafter. Natalizumab must be discontinued at the first sign of PML or other opportunistic infection developing; treatment may resume if this diagnosis is excluded, but should be permanently discontinued if confirmed.

Patients who were previously taking interferon beta or glatiramer acetate may switch directly to natalizumab provided there are no treatment-related adverse effects such as neutropenia; blood counts must return to normal before starting natalizumab. Patients who have been receiving immunosuppressants such as azathioprine and cyclophosphamide must not start natalizumab until it has been confirmed that they are no longer immunocompromised. Likewise, the pharmacodynamic effects of natalizumab remain for about 12 weeks after stopping treatment, and therefore a wash-out period may be appropriate on stopping natalizumab before giving immunosuppressive drugs.

Natalizumab 300 mg is given by intravenous infusion once every 4 weeks. The dose is diluted in 100 mL of sodium chloride 0.9% and given over about 1 hour. The patient should be observed during the infusion and for a further hour after it is complete; the infusion should be stopped if a hypersensitivity reaction occurs and treatment with natalizumab permanently discontinued. Treatment should also be discontinued if there is evidence of persistent raised antibodies to natalizumab since these reduce efficacy and increase the risk of hypersensitivity reactions. Continuation of therapy in multiple sclerosis patients who have shown no benefit after 6 months should be reconsidered. In the treatment of Crohn's disease, natalizumab should be stopped if patients have not obtained therapeutic benefit after 12 weeks of induction ther-