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HEALTH TECHNOLOGY BRIEFING
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Natalizumab (subcutaneous injection) for highly active relapsing remitting multiple sclerosis

NIHRIO ID	30451	**NICE ID**	10551
Developer/Company	Biogen	**UKPS ID**	659490

Licensing and market availability plans	Currently in phase III/II clinical trials.

SUMMARY

Natulizumab administered as a subcutaneous formulation is currently in clinical development for highly active relapsing remitting multiple sclerosis (RRMS). RRMS is characterised by periods of exacerbation of symptoms (relapses) followed by unpredictable periods of stability (remission). Highly active disease is characterised by an unchanged/increased relapse rate or by ongoing severe relapses compared with the previous year. Natalizumab is currently administered intravenously for patients with multiple sclerosis, however subcutaneous natalizumab injections require less time and are easier to perform.

Natalizumab is a type of biologic drug which binds to immune cells in the blood stream, preventing them from passing from the blood into the central nervous system where they can damage nerves. If licensed, subcutaneous natalizumab will offer more convenient treatment option for patiets with highly active RRMS.

PROPOSED INDICATION

Highly active relapsing remitting multiple sclerosis (RRMS).[a]

TECHNOLOGY

DESCRIPTION

Natalizumab (Tysabri) is a selective adhesion-molecule inhibitor and binds to the α4-subunit of human integrins, which is highly expressed on the surface of all leukocytes, with the exception of neutrophils. Specifically, natalizumab binds to the α4β1 integrin, blocking the interaction with its cognate receptor, vascular cell adhesion molecule-1 (VCAM-1), and ligands osteopontin, and an alternatively spliced domain of fibronectin, connecting segment-1 (CS-1). Natalizumab blocks the interaction of α4β7 integrin with the mucosal addressin cell adhesion molecule-1 (MadCAM-1). Disruption of these molecular interactions prevents transmigration of mononuclear leukocytes across the endothelium into inflamed parenchymal tissue. A further mechanism of action of natalizumab may be to suppress ongoing inflammatory reactions in diseased tissues by inhibiting the interaction of α4-expressing leukocytes with their ligands in the extracellular matrix and on parenchymal cells. As such, natalizumab may act to suppress inflammatory activity present at the disease site, and inhibit further recruitment of immune cells into inflamed tissues.[1]

Natulizumab subcutaneous formulation is currently in clinical development for highly active RRMS. In the Phase 2 Clinical Trial REFINE (NCT01405820), natalizumab was administered via subcutaneous injection 300 mg every 4 weeks for 60 weeks.[2]

INNOVATION AND/OR ADVANTAGES

Subcutaneous natalizumab injections reguire less time and are easier to perform compared to intravenous administration of the drug.[3] However, observation is required for the first 6 doses for any signs of injection reactions, such as hypersensitivity.[b]

A study of various administration routes of natalizumab demonstrated that a single natalizumab dose administered provided greater relative bioavailability by the subcutaneous route (57.1% to 71.3%) than by the intramuscular route (48.7%). Also, administration site reaction incidence was lower for those receiving subcutaneous injection (SC) than for for those receiving intravenous (IV).[3]

In the phase 1 DELIVER study (NCT00559702), SC administration of natalizumab 300 mg resulted in comparable pharmacokinetic (PK) and pharmacodynamic (PD) profiles, safety, tolerability, and immunogenicity to that of IV natalizumab. Similarly, the phase 2 REFINE study (101MS206) showed that natalizumab 300 mg SC every 4 weeks (Q4W) was comparable to standard 300 mg IV Q4W dosing with respect to clinical and MRI efficacy, PK/PD, immunogenicity, and safety.[3]

Lastly, in terms of the route of administration, data support that SC administration is simpler than IV infusions, can reduce drug delivery-related healthcare costs and resources, and is largely preferred by both patients and healthcare professionals.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

In the EU/UK, natalizumab is licensed for multiple sclerosis (via IV injection).[5] Common side effects include: alopecia, anaemia, anaphylactic reaction, arthralgia, asthenia, conjunctivitis, constipation, cough, depression, diarrhoea, fever, headache, hypersensitivity (discontinue permanently),

[a] Information provided by Biogen on UK PharmaScan
[b] Information provided by Biogen

increased risk of infection, infusion related reaction, leucopenia, myocardial infarction, neutropenia, night sweats, pain, thrombocytopenia, vomiting. [6]

Natalizumab is also in Phase II trials for high risk acute graft-versus-host disease and pulmonary metastatic osteosarcoma.[7]

PATIENT GROUP

DISEASE BACKGROUND

Multiple sclerosis (MS) is a condition that can affect the brain and spinal cord, causing a wide range of potential symptoms, including problems with vision, arm or leg movement, sensation or balance.[8] The clinical course of MS is highly heterogeneous. Approximately 85% of patients present with a RRMS. A review of risk factors associated with RRMS found that exposure to Epstein-Barr virus appear to increase the risk of RRMS.[9]

RRMS is the most common pattern of the disease. It is characterised by periods of exacerbation of symptoms (relapses) followed by unpredictable periods of stability (remission). The severity and frequency of relapses varies greatly between patients, but on average occurs once or twice per year. This clinical pattern often develops into secondary-progressive multiple sclerosis, with progressive disability unrelated to relapses. Most patients develop secondary progressive disease 6–10 years after onset. Highly active disease is characterised by an unchanged/increased relapse rate or by ongoing severe relapses compared with the previous year.[10]

Some of the most common symptoms in RRMS around the time of diagnosis are problems with eyesight, slowed thinking (cognitive symptoms) and unusual feelings in the skin (such as pins and needles or numbness). Fatigue is also very common. This is not normal tiredness, but a mental or physical exhaustion out of all proportion to the activity carried out.[11] As these patients experience different severities/symptoms of the disease, it is difficult to understand how the disease directly affects their quality of life. Nonetheless, it is clear from the symptoms mentioned above, that the day-to-day activity of people with RRMS is hindered, and thus it can be assumed that the quality of life of people with RRMS is worse than of healthy people.

CLINICAL NEED AND BURDEN OF DISEASE

In England, MS estimated prevalence is 190 cases per 100,000 population, with 105,800 individuals in England.[12] About 85% of patients develop RRMS, which means that the prevalence of RRMS is approximately 162 cases per 100,000 which equals to 89,930 people in England living with the condition. It is estimated that between 8 and 11 new cases of MS are diagnosed each year in England per 100,000 population.[12]

According to Hospital Episodes Statistics (HES) (ICD-10: G35-G37) data in 2018-2019, in England, there were 53,434 finished consultant episodes (FCEs), 49,768 admissions, resulting in 67,411 FCE bed days and 44, 352 day cases of primary diagnosis of demyelinating diseases (including multiple sclerosis) of the central nervous system.[13]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There is currently no cure for MS, but it is possible to treat the symptoms with medicines and other treatments. This may include a neurologist (specialist in treating conditions of the nervous system), a physiotherapist, a speech and language therapist, and a number of other professionals.[14]

Teriflunomide and dimethyl fumarate are treatment options for patients with active disease. They may be preferred due to their oral route of administration. There is insufficient evidence for the use of either drug to treat highly active or rapidly-evolving severe RRMS.[10]

Official guidelines recommend that everyone with MS has a review with their specialist at least once a year. It should be decided together with a specialist what the treatment plan should be.[15]

CURRENT TREATMENT OPTIONS

Other pharmacological treatments for highly active RRMS in the UK include:[16]

- Alemtuzumab
- Cladribine
- Fingolimod
- Natalizumab IV
- Ocrelizumab (for primary progressive MS)
- Siponimod (secondary progressive MS)

PLACE OF TECHNOLOGY

If licensed, SC natalizumab will offer an additional treatment option for patiets with highly active RRMS.

CLINICAL TRIAL INFORMATION

Trial	**REFINE; NCT01405820; EudraCT-2010-024000-10;** A Randomized, Blinded, Parallel-Group, Phase 2 Study Exploring the Safety, Tolerability, and Efficacy of Multiple Regimens of Natalizumab in Adult Subjects With Relapsing Multiple Sclerosis **Phase II** – completed **Locations:** 5 EU countries, not incl. UK **Study completion date**: October 2014
Trial design	Randomised, parallel assignment, double-blinded (participant, investigator)
Population	N= 290; documented diagnosis of RRMS
Intervention(s)	- Natalizumab 300mg every 4 weeks (SC) - Natalizumab 300mg every 12 weeks (IV) - Natalizumab 300 mg every 12 weeks (SC) - Natalizumab 150 mg every 12 weeks (IV) - Natalizumab 150 mg every 12 weeks (SC)
Comparator(s)	Natalizumab 300 mg every 4 weeks (IV)
Outcome(s)	Cumulative number of combined unique active lesions [Time frame: up to week 60]
Results (efficacy)	Unpublished. See trial record for efficacy results

Results (safety)	Unpublished. See trial record for safety results

ESTIMATED COST

Cost of natalizumab SC was confidential at the time of producing this briefing.

The NHS indicative price for natalizumab 300mg IV, is £1,130 per 300mg administration.[17]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Ozanimod for treating relapsing multiple sclerosis (GID-TA10299). Expected date of issue to be confirmed.
- NICE technology appraisal guidance. Peginterferon beta-1a for treating relapsing–remitting multiple sclerosis (TA624). February 2020.
- NICE technology appraisal guidance. Cladribine for treating relapsing–remitting multiple sclerosis (TA616). December 2019.
- NICE technology appraisal guidance. Ocrelizumab for treating relapsing–remitting multiple sclerosis (TA533). July 2018.
- NICE technology appraisal guidance. Beta interferons and glatiramer acetate for treating multiple sclerosis (TA527). June 2018.
- NICE technology appraisal guidance. Alemtuzumab for treating relapsing–remitting multiple sclerosis (TA312). May 2014.
- NICE technology appraisal guidance. Dimethyl fumarate for treating relapsing-remitting multiple sclerosis (TA320). August 2014.
- NICE technology appraisal guidance. Teriflunomide for treating relapsing–remitting multiple sclerosis (TA303). January 2014.
- NICE technology appraisal guidance. Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis (TA254). April 2012.
- NICE technology appraisal guidance. Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis (TA127). August 2007.
- NICE clinical guideline. Multiple sclerosis in adults: management (CG186). October 2014.
- NICE quality standard. Multiple sclerosis (QS108). January 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies (NHS England Reference: 170079ALG). London: NHS England; 2019.

OTHER GUIDANCE

- None identified

ADDITIONAL INFORMATION

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