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Fingolimod (Gilenya) oral formulation for multiple sclerosis in paediatric patients (aged 10 – 17 years)

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LAY SUMMARY

Multiple sclerosis is an inflammatory condition of the central nervous system. Whilst it is unclear how this is caused, there are a number of associated symptoms ranging from visual disturbances to bowel dysfunction. Multiple sclerosis is the most common cause of non-traumatic neurological disability in young adults. Younger patients (paediatric) compared to their older counterparts tend to experience higher frequency of relapses and greater disability, however, licensed treatment options are currently not available specifically for paediatric MS.

The current treatment is already licensed in adults, but is currently in a phase III trial for the treatment of multiple sclerosis in paediatric patients. Fingolimod will be administered orally once daily at a dose of either 0.5 mg or 0.25 mg depending on the patient's body weight. If marketed this will become the first treatment with a specific licensed indication for paediatric multiple sclerosis.

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TARGET GROUP

Multiple sclerosis (MS) in paediatric patients (aged 10-17 years), relapsing – first line

TECHNOLOGY

DESCRIPTION

Fingolimod (Gilenya) is a sphingosine 1-phosphate receptor modulator. Fingolimod is metabolised by sphingosine kinase to the active metabolite fingolimod phosphate. Fingolimod phosphate binds at low nanomolar concentrations to sphingosine 1-phosphate (S1P) receptor 1 located on lymphocytes, and readily crosses the blood-brain barrier to bind to S1P receptor 1 located on neural cells in the central nervous system (CNS). By acting as a functional antagonist of S1P receptors on lymphocytes, fingolimod phosphate blocks the capacity of lymphocytes to egress from lymph nodes, causing a redistribution, rather than depletion, of lymphocytes.[1,2]

Fingolimod is indicated in the EU as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups:

- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy
  or
- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.[2]

For the treatment of paediatric multiple sclerosis, the current product is in a phase III clinical trial. Fingolimod is administered orally once daily at a dose of either 0.5 mg or 0.25 mg (depending on patient's body weight) with the aim to achieve systemic exposure in range of that in adults at the licensed 0.5 mg dose.[3]

INNOVATION and/or ADVANTAGES

As there is a demand for treatment options for paediatric patients with multiple sclerosis, safety data is crucial, which the current study intends on providing.[25] The current treatment will therefore be novel as it will be the first marketed treatment for multiple sclerosis in specifically, a paediatric population. It will also be the first oral treatment available for paediatric patients with multiple sclerosis. Currently, only injectable treatments are used in clinical practice to treat paediatric patients with multiple sclerosis.

DEVELOPER

Novartis Pharmaceuticals UK Ltd.

AVAILABILITY, LAUNCH or MARKETING

In phase III trials

PATIENT GROUP

BACKGROUND

MS is an acquired chronic autoimmune inflammatory condition of the CNS.[4] The precise cause of MS remains unknown, but evidence suggests that it is caused by a complex interplay of epigenetic, environmental, and genetic factors that provoke an autoimmune inflammatory response.[5] This results in areas of demyelination, gliosis, and secondary neuronal damage throughout the CNS.[4] The usual flow of nerve impulses along nerve fibres (axons) is interrupted or distorted. This results in the wide variety of symptoms and reduced or absent neurological function, which depends upon the part or parts of the CNS that are affected.[6] Patients with MS typically develop symptoms any time from 20 to 50 years of age, experiencing cognitive, visual and sensory disturbances, limb weakness, gait problems, and bladder and bowel dysfunction.[7] Whilst MS usually starts in adulthood, it has become increasingly common in younger patients, leading to the diagnosis of Paediatric Onset MS (POMS) in patients under the age of 18 years.[8]

Symptoms presented are typically similar to those experienced by adults, however an acute polysymptomatic onset with encephalopathy, and frequent initial presentation with symptoms indicating cerebellar or brainstem involvement are considered standard of diagnosis.[9] Furthermore very young patients (under 12 years) are likely to present with a polysymptomatic onset, a high number of relapses, a more severe clinical involvement, and a worse prognosis, which creates limitations in the adult diagnostic criteria often applied to those under 18 years of age.[10,11] Despite a high relapse rate, the time to reach mild or severe disability is longer in POMS than MS, with an estimated delay of 10 years.[12]

MS has an unpredictable course with variable disease severity and progression. The most common pattern of disease is relapsing remitting MS (RRMS), where periods of stability (remission) are followed by episodes when there are exacerbations of symptoms (relapses). About 80-85% of people with MS have RRMS at onset and around two-thirds of these patients will subsequently develop secondary progressive MS, where there is a gradual accumulation of disability unrelated to relapses, which become less frequent or stop completely. Approximately 10 to 15% of people with MS present with primary progressive MS where symptoms gradually develop and worsen with no distinct relapses and remissions.[12]

Patients with a younger age at onset of MS, a longer disease duration and a higher disability are thought to be most at risk of cognitive dysfunction.[13,14] Cognitive dysfunction is also present in 30-50% of cases of POMS.[13] Furthermore the most frequent functions affected are attention, language (receptive, verbal fluency and naming); visual-spatial and motor functions, spatial memory, executive functions and abstract reasoning.[11] Compared to adult MS, paediatric patients have more pronounced language and information processing speed impairments[13] and ultimately reach permanent disability at a younger age.[15]

CLINICAL NEED and BURDEN OF DISEASE

In England the prevalence of MS is estimated to be 164 per 100,000 population, which equates to around 89,000 people with MS, and there are approximately 5000 people diagnosed each year with the condition.[16] An estimated 3–10% of all patients with MS have onset before the age of 18 years.[9] As in adult MS, females are more frequently affected than males with a ratio of about 3:1, but in patients less than 10–12 years this ratio is about 1:1.[17] The mean disease duration associated with a

50% risk of secondary-progressive MS is 23 years in patients with paediatric-onset, and the risk of secondary-progressive MS was also associated with a high frequency of relapse and shorter intervals between attacks in the first few years of disease.[18]

MS is the most common cause of non-traumatic neurological disability in young adults and causes high levels of disability and impaired quality of life for prolonged periods.[6] Up to 35% of paediatric MS cases have some identifiable cognitive dysfunction at the time of diagnosis, and at least one-half of children continue to accrue cognitive deficits within the first 5 years after disease onset.[19] This cognitive decline limits social, academic and recreational activities which consequently negatively impacts quality of life.[11] Approximately 50% of patients require a walking aid within 15 years of disease onset,[20] and the disease is associated with a high rate of unemployment in early adulthood, as only 25% of patients with MS are estimated to be in employment.[21]

In 2015-16, there were 50,252 hospital admissions for MS (ICD-10 G35) in England, accounting for 52,829 finished consultant episodes and 54,025 bed days. During this time, 302 hospital admissions were recorded in patients aged 10-17 years old.[22] In 2015, 1295 deaths due to MS were registered in England and Wales; none of these were in people under the age of 25.[23]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Multiple sclerosis - interferon beta, glatiramer acetate (review TA32) (TA809). Expected publication date TBC.
- NICE technology appraisal in development. Multiple sclerosis cladribine (TA64). Expected February 2018.
- NICE technology appraisal. Daclizumab for treating relapsing–remitting multiple sclerosis (TA441). April 2017.
- NICE technology appraisal. Dimethyl fumarate for treating relapsing-remitting multiple sclerosis (TA320). August 2014.
- NICE technology appraisal. Alemtuzumab for treating relapsing-remitting multiple sclerosis (TA312). May 2014.
- NICE technology appraisal. Teriflunomide for treating relapsing-remitting multiple sclerosis (TA303). January 2014.
- NICE technology appraisal. Fingolimod for the treatment of highly active relapsing- remitting multiple sclerosis (TA254). April 2012.
- NICE clinical guidance. Multiple sclerosis in adults: management (CG186). October 2014.
- NICE quality standard. Multiple sclerosis (QS108). January 2016.
- NICE interventional procedure guidance. Percutaneous venoplasty for chronic cerebrospinal venous insufficiency for multiple sclerosis (IPG420). March 2012.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. Clinical Commissioning Policy: Fampridine for Multiple Sclerosis (adults). 16010/P. July 2016.

- NHS England. Service Specification: Paediatric Onset Multiple Sclerosis. E09/S/(HSS) tba. March 2016.
- NHS England. Integrated Impact Assessment Report for Clinical Service Specifications: Paediatric Onset Multiple Sclerosis. E09/S/(HSS)/tba. March 2016.
- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/S/a.
- NHS England. Clinical Commissioning Policy: Disease Modifying Therapies for Patients with Multiple Sclerosis. NHSCB/D04/P/b. May 2014.
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OTHER GUIDANCE

- European Society for Blood and Marrow Transplantation. SCT for severe autoimmune diseases: consensus guidelines for immune monitoring and biobanking. 2015.
- Association of British Neurologists. Position statement on the use of AHSCT in MS. www.theabn.org/resources/abn/a/abn-statement-on-autologous-haematopoietic-stem-celltreatment-of-multiple-sclerosis.html Accessed 1 September 2016.
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CURRENT TREATMENT OPTIONS

Care for people with MS should adopt a coordinated multidisciplinary approach involving consultant neurologists, specialist nurses, physiotherapists, occupational therapists, dieticians, social care and continence specialists, and speech and language therapists.[7] In MS, the majority of pharmacological treatments, physical therapy and psychological therapy is directed at the management of specific symptoms, such as incontinence, fatigue, pain and depression.[24,25] In addition to management of symptoms, patients with secondary progressive MS with relapse can be treated with high-dose steroids.[8,26].

Immune modulating disease modifying therapies are used with a view to changing the long-term course of MS and work by reducing the number and severity of relapses.[7] As a result they have only been found to be effective for people with RRMS and for some people with secondary progressive MS who continue to relapse.[5] Interferon β 1b is licensed in the EU for the treatment of secondary progressive MS with active disease, evidenced by relapses[27].

In paediatrics, a diagnosis of MS can only be confirmed when disorders that mimic MS are excluded. Depending on the clinical scenario, some disorders to consider include acute disseminated encephalomyelitis (ADEM), small vessel CNS vasculitis, lupus, CNS infection, and neuromyelitis optica (NMO). Exclusion of MS mimics is especially important when considering selection of appropriate disease modifying therapy as patients with different relapsing disorders may respond poorly to some of the approved MS therapies.[19]

The currently licensed disease-modifying treatments for RRMS in adults include:[28]

- Alemtuzumab
- Natalizumab
- β-interferons
- Glatiramer acetate
- Teriflunomide
- Dimethyl fumarate
- Fingolimod
- Daclizumab

The above treatment options are based on an adult approach to MS treatment as studies into paediatric MS are scarce. Treatment is considered when an exacerbation causes symptoms that are associated with impairment, such as limited mobility or vision.[11]

EFFICACY and SAFETY	
Trial	GDCT0195159, NCT01892722, CFTY720D2311; children aged 10-17 years; fingolimod vs interferon beta-1a i.m; phase III
Sponsor	Novartis Pharmaceuticals
Status	Ongoing
Source of Information	Trial registry[3]
Location	20 EU countries, incl UK, USA, Canada, Mexico, Brazil, Venezuela, South Africa and Australia
Design	Randomised, placebo-controlled, double-blind study
Participants	n=215, aged 10 to 17 years, relapsing multiple sclerosis; first line
Schedule	Double-dummy masking is required to blind formulations: Patients in the fingolimod arm will also take weekly placebo i.m. injections (syringes matched in appearance to the active interferon beta-1a i.m. syringes). Fingolimod will be administered orally once daily at a dose of either 0.5 mg or 0.25 mg (depending on patient's body weight) with the aim to achieve systemic exposure in range of that in adults at the licensed 0.5 mg dose.
Follow-up	Not reported
Primary Outcomes	Frequency of relapses in patients treated for up to 24 months expressed as annualised relapse rate
Secondary Outcomes	To evaluate the safety of fingolimod relative to IFN β-1a in child/adolescent MS subjects Number of new/newly enlarged T2 (n/neT2) lesions - 24 months Frequency and nature of adverse events as a measure of safety and tolerability - 24 months Pharmacokinetics (Cavg)of fingolimod and fingolimod-P - 24 months To evaluate the effect of fingolimod relative to IFN β-1a in children/adolescent MS patients on T1 Gd-enhancing lesions on brain MRI.

	Proportion of relapse free patients and time to first relapse in fingolimod treated patients versus IFN β-1a To study the pharmacokinetic/pharmacodynamic relationship for key efficacy and safety outcomes in children/adolescent MS patients treated for up to 24 months
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion estimated Q4 2017. Extension phase to complete by March 2023.

ESTIMATED COST and IMPACT

COST

Fingolimod is currently licensed for adults with MS in capsule form; 7 x 500 microgram capsules = £367.50 and 28 x 500 microgram capsules = £1470.00.[29]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Other: *improve patient convenience*

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☒ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☒ Other: *uncertain unit cost compared to existing treatments*

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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