Provision of miglustat for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease in Wales

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Recommendation:
Miglustat is recommended as an option for use within NHS Wales for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease.

Background

Miglustat for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C (NPC) disease was assigned orphan medicine status in 2006 by the European Medicines Agency and licensed in 2009 (Miglustat EPAR). The All Wales Medicines Strategy Group (AWMSG) issued a statement of advice for miglustat (Zavesca®) in 2009; due to the absence of a submission from the market authorisation holder miglustat could not be endorsed for the treatment of NPC. Miglustat was commissioned and routinely available until January 2023, via the Welsh Health Specialised Services Committee (which has now become the Joint Commissioning Committee, JCC). However, following a review, commissioning was withdrawn due to an absence of positive advice from either the National Institute for Health Care and Excellence (NICE) or AWMSG. Miglustat does not meet the criteria for NICE appraisal. It is commissioned by NHS England under a legacy agreement (NHS England).

Miglustat is the only licensed medicine for the treatment of NPC. JCC has approached AWTTC to provide advice for miglustat, highlighting the unmet need which exists for patients with NPC. Clinicians have confirmed the need for patient access to miglustat in Wales. They highlight that a number of studies conclude that miglustat has a beneficial effect in the treatment of NPC. Since the initial licence other companies have obtained licences for use of miglustat in this indication.

The condition and clinical guidelines

NPC is a very rare, invariably progressive and eventually fatal neurodegenerative disorder characterised by impaired intracellular lipid trafficking (Miglustat summary of product characteristics). The age of onset of NPC can range from the perinatal period to adulthood, with symptoms varying with age of onset (Pineda et al, 2019). Early-onset NPC tends to be more severe and rapidly progressive than adult-onset NPC. Patients who develop NPC during early infancy often present with visceral manifestations such as splenomegaly, hepatomegaly, and cholestasis, with varying degrees of neurologic signs and symptoms including delayed developmental milestones, hypotonia (decreased muscle tone), and dystonia (poor muscle tone). In adolescence or adulthood, patients tend to present with varying combinations of progressive neurologic deficits such as ataxia (difficulty coordinating movement), dystonia, and/or dementia or major psychiatric illness. Supranuclear saccade palsy (eye movement abnormality) is the most common neurologic symptom, and is often overlooked during the initial differential diagnosis (Pineda et al, 2019).

Gastrointestinal disturbances such as diarrhoea, flatulence and abdominal pain/discomfort have consistently been reported as the most frequent adverse events associated with miglustat during clinical trials and in real-world clinical practice settings. These adverse events are generally mild or moderate in severity, occurring mostly during the initial weeks of therapy (Belmatoug et al, 2011).

Glycosphingolipids build up within cells in the brain and elsewhere in the body (Miglustat EPAR public summary) Miglustat inhibits glucosylceramide synthase which catalyses the first committed step of glycosphingolipid synthesis (Patterson et al 2007). In consensus guidelines 62% of experts in 2018 agreed that patients with a confirmed diagnosis of NPC should be considered for miglustat therapy (Geberhiwot et al, 2018). Paediatric patients in Wales may be referred to the outreach clinics of the Birmingham or Manchester lysosomal storage disorder clinics for multi-disciplinary treatment care (seen every 6 months), alternatively, they may be seen by the individual specialities within Wales. Adult patients would be managed in Wales. The consensus group were mainly in agreement that miglustat would not be offered to pre-symptomatic patients or those with only spleen or liver enlargement. There was agreement not to start miglustat in those with advanced neurological disease/dementia.

Incidence

The incidence of NPC has been reported as 1 in 120,000 (NPUK) and (Mengel et al, 2013) and 1:89,000 (Patterson et al, 2020) suggesting approximately 1 new NPC case in Wales once every 3-4 years. [Confidential information removed]

Clinical effectiveness

In the pivotal study, NPC patients aged 12 years or older were randomly assigned to receive either miglustat (n=20) or standard care (n=9) for 12 months. Study participants could continue to take medications prescribed by their principal care physician. These included analgesics, antibiotics, anti-diarrhoeal agents, sedative or hypnotics, antiepileptic medicines, medicines used to treat dystonia, or other agents used to treat the symptoms of NPC. The primary endpoint was horizontal saccadic eye movement (HSEM) velocity, based on its correlation with disease progression. At 12 months, HSEM velocity had improved in patients treated with miglustat versus those receiving standard care; results were significant when patients taking benzodiazepines were excluded (p=0.028). Children (n = 12) under 12 years of age showed an improvement in HSEM velocity of similar size at 12 months. Improvement in swallowing capacity, stable auditory acuity, and a slower deterioration in ambulatory index were also seen in treated patients older than 12 years (Patterson et al 2007, Miglustat SPC). Further studies showed Miglustat stabilized neurological disease progression in paediatric patients with NPC, with comparable safety and tolerability to that observed in adults and juveniles (Patterson et al, 2010). Long term NPC registry studies found miglustat improved survival versus no treatment (Patterson et al, 2020) and reduced disability score worsening in juvenile and infant patients (Pineda et al, 2019), (Patterson et al, 2020).

Clinical opinion is that miglustat slows neurological progression in NPC but does not halt or reverse it. Several patients were stabilised on miglustat for many years in NHS England which allowed them to participate in clinical trials of potentially more

effective treatment options. Clinicians are proactive in stopping miglustat when it is clear it is no longer benefitting the patient.

Cost-effectiveness

An AWTTC literature search identified one cost-utility analysis, conducted in the Republic of Serbia, comparing miglustat with symptomatic therapy in patients with NPC (Gutic 2022). The discrete event simulation model adopted a lifetime time horizon, a health insurance perspective and applied an annual discount rate of 1% on both costs and quality-adjusted life years (QALYs). Miglustat generated between 1.14 additional QALYs in the early infantile cohort (onset < 2 years) and 3.62 additional QALYs in the adolescent/adult cohort (onset > 15 years of age). The base case incremental cost-effectiveness ratios (ICERs) did not support miglustat as a cost-effective treatment option. Notably, there are a number of limitations in applying these analyses to the UK setting. No publications were identified evaluating the cost-effectiveness of miglustat in the UK setting.

Budget impact

The recommended dose of miglustat is 200mg three times daily in adults. Several companies have licences for the use of miglustat to treat NPC. An average price for four companies supplying miglustat is £3,702 for 84 x 100mg capsules (range £3,442 to £3.934). This average cost is consistent with an annual cost of £99,954 for an adult. For a child with body surface area >0.73m^2 – 0.88m^2, the annual cost is £51,828.