Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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migalastat, 123mg hard capsules (Galafold®) SMC No. (1196/16)

Amicus Therapeutics

07 October 2016

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

migalastat (Galafold®) is accepted for restricted use within NHS Scotland.

Indication under review: long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation.

SMC restriction: in males with classic mutations (leucocyte enzyme activity <1%) treatment should commence at diagnosis; in females and those males with later onset mutations with higher levels of leucocyte enzyme activity, treatment should commence when patients experience uncontrolled pain, evidence of renal, cardiac or neurovascular disease, or gastrointestinal symptoms that significantly reduce quality of life.

In an 18-month, randomised, phase III study, migalastat was comparable to enzyme replacement therapy, measured by mean annualised rate of change in glomerular filtration rate.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of migalastat. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation.

Dosing Information

Migalastat 123mg (1 capsule) orally, swallowed whole, once every other day at the same time of day. Migalastat should not be taken within two hours before and after food.

Treatment with migalastat should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of Fabry disease. Migalastat is not intended for concomitant use with enzyme replacement therapy.

Product availability date

26 May 2016
Migalastat meets SMC ultra-orphan criteria for this indication.

Summary of evidence on comparative efficacy

Fabry disease is a rare X-linked lysosomal storage disorder affecting both males and females. It is caused by mutations in the GLA gene which lead to a deficiency of the lysosomal enzyme alfa-galactosidase A (α-Gal A). This enzyme is required for glycosphingolipid substrate (e.g. globotriaosylceramide [GL-3], globotriaosylsphingosine [lyso-Gb_3]) metabolism. The progressive accumulation of substrate in vulnerable organs and tissues results in the morbidity and mortality associated with Fabry disease. Migalastat is a pharmacological chaperone; it binds to the active site of amenable mutations of α-Gal A on the endoplasmic reticulum to facilitate their proper trafficking to lysosomes resulting in restoration of α-Gal A activity and a reduction of substrate.[1,2]

The submitting company requested that SMC considers migalastat when positioned for use as per the UK Adult Fabry Disease Standard Operating Procedures. In males with classic mutations (leucocyte enzyme activity <1%), treatment should commence at diagnosis. In females and those males with later onset mutations with higher levels of leucocyte enzyme activity, treatment should commence when patients experience uncontrolled pain, evidence of renal, cardiac or neurovascular disease, or gastrointestinal symptoms that significantly reduce quality of life.

Evidence to support the marketing authorisation comes from two phase III randomised studies, ATTRACT and FACETS, conducted in patients over 16 years of age with a confirmed diagnosis of Fabry disease, GLA mutations that were responsive to migalastat on the human embryonic kidney (HEK)-assay and with a glomerular filtration rate (GFR) of ≥30mL/min/1.73m.[2,3]

ATTRACT was an open-label study designed to compare migalastat with enzyme replacement therapy (ERT) in 60 patients who had been receiving ERT for at least 12 months. Patients were required to be eligible for treatment according to the European Fabry Working Group consensus document. Patients were stratified according to gender and proteinuria (<100mg/24h versus

≥100mg/24h) then randomised in a 1.5:1 ratio to receive migalastat 123mg every other day or to continue with ERT (agalsidase alfa or agalsidase beta, administered according to approved prescribing information) for 18 months. Those who completed the study were eligible to enter the ongoing 12-month, open-label extension study where all patients are receiving migalastat.[2, 4]

The co-primary efficacy outcomes were the annualised rate of change in GFR estimated by the Chronic Kidney Disease Epidemiology Collaboration equation ($eGFR_{CKD\text{-}EPI}$) and measured by the plasma clearance of unlabelled iohexol ($mGFR_{iohexol}$) in the modified intention-to-treat (mITT) population. This included all randomised patients with mutations amenable to migalastat in the validated Good Laboratory Practice (GLP) HEK-assay (Migalastat Amenability Assay), who had received at least one dose of study drug and had a baseline and a post-baseline efficacy measure of $mGFR_{iohexol}$ and $eGFR_{CKD\text{-}EPI}$. The pre-specified criteria to declare comparability of the two treatments were:

- the difference in least squares mean annualised rate of change in GFR was ≤2.2mL/min/1.73m^2
- a >50% overlap of the 95% confidence intervals (CI) for migalastat and ERT.[2]

Table 1 contains the results of the co-primary outcomes. Comparability was considered to be demonstrated according to the pre-specified criteria.[2]

Table 1. ATTRACT co-primary outcomes: least squares mean annualised rate of change from baseline to month 18 [2, 5]

Primary outcome	**Migalastat (n=34)**	**ERT (n=18)**
Least squares mean annualised rate of change from baseline to month 18 in $eGFR_{CKD\text{-}EPI}$	-0.40mL/min/1.73m^2 (95% CI: -2.272 to 1.478)	-1.03mL/min/1.73m^2 (95% CI: -3.636 to 1.575)
Least squares mean annualised rate of change from baseline to month 18 in $mGFR_{iohexol}$	-4.4mL/min/1.73m^2 (95% CI: -7.651 to -1.056)	-3.2mL/min/1.73m^2 (95% CI: -7.809 to 1.334)

ERT: enzyme replacement therapy, CI: confidence interval, $eGFR_{CKD\text{-}EPI}$: glomerular filtration rate estimated by the Chronic Kidney Disease Epidemiology Collaboration equation, $mGFR_{iohexol}$: glomerular filtration rate measured by the plasma clearance of unlabelled iohexol

Secondary outcomes included mean change from baseline to month 18 in 24-hour urine protein, left ventricular mass index (LVMi) measured by echocardiography and plasma lyso-Gb_3, see table 2. The proportion of patients experiencing a pre-specified renal, cardiac or cerebrovascular outcome was 29% in the migalastat group and 44% in the ERT group. Two patients in the ERT group had both a renal and a cardiovascular event.[2]

Table 2. ATTRACT selected secondary outcomes: mean change from baseline to month 18.[2, 5]

Outcome (±standard deviation)	Migalastat	ERT
Mean change from baseline to month 18 in 24-hour urine protein, mg/day	49 (±200)	194 (±691)
Mean change from baseline to month 18 in urine albumin:creatinine ratio, mg/mmol	5.8 (±20)	14 (±40)
Mean change from baseline to month 18 in LVMi, g/m^2	-6.6 (±12)	-2.0 (±15)
Mean change from baseline to month 18 in plasma lyso-Gb_3, nanomol/L	1.7 (±5.5)	-1.9 (±4.8)

ERT: enzyme replacement therapy, LVMi: left ventricular mass index, lyso-Gb_3: globotriaosylsphingosine

Health-related quality of life was assessed using the Short Form Health Survey with 36 questions, version 2 (SF-36v2) and the severity component of the Brief Pain Inventory short form (BPI). In both treatment groups, there were no important changes from baseline in SF-36v2 or BPI at any time point.[2]

The FACETS study had a six-month, double-blind, randomised, placebo-controlled treatment phase (stage 1) and a six-month, open-label, follow-up period (stage 2). Patients who completed the study were eligible to enter a further 12-month open-label extension study. Eligible patients were either ERT-naïve or had not received ERT in the six months before screening and had urine GL-3 concentration ≥4 times the upper limit of normal at screening. Patients were stratified by gender then randomised to receive migalastat 123mg orally once every other day (n=34) or placebo (n=33) during stage 1. All patients could receive migalastat 123mg orally once every other day during stage 2.[2,3]

The primary endpoint for stage 1 was the proportion of patients with a ≥50% reduction from baseline to month six in the average number of GL-3 inclusions per kidney interstitial capillary measured in the ITT population. This was achieved by 38% (13/34) patients in the migalastat group and 27% (9/33) patients in the placebo group, p=0.3. The mean change from baseline (standard deviation, SD) in the average number of GL-3 inclusions per kidney interstitial capillary was -8.0% (±105) and 13% (±90) for the migalastat and placebo groups respectively, p=0.097.[2]

A post-hoc analysis was performed in 50 patients who had GLP HEK-assay (Migalastat Amenability Assay) amenable mutations. A change from baseline analysis showed greater reduction in the average number of GL-3 inclusions per interstitial capillary in patients treated with migalastat, (-0.25 [standard error of the mean [SEM]] ±0.10) compared with placebo (+0.07 [±0.13]), p=0.008.[2]

Secondary outcomes included change from baseline in plasma lyso-Gb_3, $eGFR_{CKD\text{-}EPI}$ and LVMi to six months. These outcomes generally supported efficacy of migalastat over placebo. Quality of life was assessed using SF-36v2, the severity component of the BPI short form and the Gastrointestinal Symptom Rating Scale (GSRS). There were some improvements, some of

which were statistically significant, in quality of life in patients taking migalastat who had GLP HEK-assay amenable mutations.[2, 3]

Summary of evidence on comparative safety

Comparative safety data are only available versus ERT from the ATTRACT study. In this study most patients reported at least one treatment emergent (TE) adverse event; 94% (34/36) of the migalastat group and 95% (20/21) of the ERT group. Serious adverse events were reported by 19% of patients taking migalastat and 33% of patients taking ERT.[2] There were more treatment-related adverse events (definitely, probably or possibly related to treatment) reported by patients taking migalastat (39%) compared with patients taking ERT (14%).[2]

The most common treatment emergent adverse events reported in patients taking migalastat and ERT were nasopharyngitis (33% versus 33%), headache (25% versus 24%), dizziness (17% versus 10%), influenza (14% versus 19%), abdominal pain (14% versus 10%), diarrhoea (14% versus 10%), nausea (14% versus 10%), back pain (11% versus 14%), upper respiratory tract infection (11% versus 5%) and urinary tract infection (11% versus 5%).[2]

Summary of clinical effectiveness issues

Fabry disease is progressive, debilitating and life-limiting. It causes many symptoms including pain, cardiovascular, renal and cerebrovascular disease and gastrointestinal dysfunction. Fabry disease can be categorised as classic or late-onset (also described as atypical or non-classic). Classic disease tends to be more clinically aggressive affecting all three major organs, heart, kidney and central nervous system. Late-onset disease may be more likely to affect only one organ and have a slower clinical course. Current treatment of Fabry disease is with ERT (agalsidase alfa or agalsidase beta) according to criteria in the UK Adult Fabry Disease Standard Operating Procedures.[2] Migalastat is considered a therapeutic advancement due to its oral administration. Migalastat meets SMC ultra-orphan criteria for this indication.

The submitting company requested that SMC considers migalastat when positioned for use as per the UK Adult Fabry Disease Standard Operating Procedures. In males with classic mutations (leucocyte enzyme activity <1%), treatment should commence at diagnosis. In females and those males with later onset mutations with higher levels of leucocyte enzyme activity, treatment should commence when patients experience uncontrolled pain, evidence of renal, cardiac or neurovascular disease, or gastrointestinal symptoms that significantly reduce quality of life.[6] These criteria are similar to the European Fabry Working Group consensus document criteria which were used to enrol patients into the ATTRACT study.[4]

The co-primary efficacy outcomes in the ATTRACT study were annualised rate of change in $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$. A large Chronic Kidney Disease Prognosis Consortium meta-analysis found that decline in $eGFR_{CKD\text{-}EPI}$ was a consistent surrogate for risk of end stage renal disease and mortality.[7] Measured GFR using iohexol is useful to confirm the results estimated using CKD-EPI.[8] A standard non-inferiority analysis was not possible due to the small sample size so pre-specified criteria were used to define comparability. The lower bound of the 95% CI for the difference between the migalastat and ERT groups in $eGFR_{CKD\text{-}EPI}$ was -2.5662, exceeding the pre-specified difference of 2.2mL/min/1.73m^2, but the EMA considered that despite this the comparability of migalastat and ERT could be assumed.

In the open-label ATTRACT study, pre-exposure to ERT could have biased against migalastat in the reporting of adverse events as only patients who could tolerate at least one year of treatment with ERT were eligible for enrolment. The 24-hour urine protein results may have been confounded by concomitant use of angiotensin converting enzyme-inhibitors, angiotensin receptor blockers or renin inhibitors. There was no reduction in proteinuria in patients treated with migalastat.[1]

The primary outcome for the FACETS study, proportion of patients with a ≥50% reduction from baseline to month six in the average numbers of GL-3 inclusions per kidney interstitial capillary, was not significantly different between migalastat and placebo. The categorical primary outcome may have overestimated response, i.e. small changes in patients with low baseline GL-3 inclusions. The low number of included patients increased the risk of a false negative result. The available literature supports a qualitative correlation between GL-3 inclusions and clinical outcome in patients with Fabry disease but a quantitative relationship has not been established. In addition, there was high variability for GL-3 inclusion scores. The EMA considered that GL-3 inclusions in renal tissue cannot be used to predict the clinical benefit of migalastat. There were some statistically significant quality of life differences between the treatment groups; however, the clinical relevance of this is uncertain.[2]

During the course of the clinical studies the HEK-assay was transferred to a third-party laboratory for analytical and GLP validation. The GLP HEK-assay (Migalastat Amenability Assay) included modifications to increase quality control, rigor, precision and consistency. In the ATTRACT study, four enrolled patients were excluded from the mITT population as they did not have amenable mutations according to the GLP HEK-assay. The FACETS ITT population included all patients; a post-hoc analysis excluded 17 patients with mutations that were not amenable according to the GLP HEK-assay. The GLP-HEK assay has a positive predictive value of 95%, meaning there is a small risk of false positive results.

The migalastat summary of product characteristics advises monitoring of renal function, echocardiographic parameters and biochemical markers every six months in patients initiated on or switched to migalastat. If there is meaningful clinical deterioration, further clinical evaluation or discontinuation of treatment should be considered. Migalastat is not indicated for use in patients with non-amenable mutations.[1,2] Migalastat is not recommended for use in patients with severe renal insufficiency (eGFR <30 mL/min/1.73m^2).[1]

There has been limited exposure of patients to migalastat beyond two years; the safety profile will be further characterised via the ongoing open-label extension studies and registry data.[2]

ERT is administered as life-long fortnightly infusions which can be burdensome for patients. The oral formulation of migalastat has advantages in terms of convenience and avoidance of infusion reactions.[5, 9, 10]

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis comparing migalastat with ERT for use in patients with Fabry disease who have amenable mutations in accordance with the UK adult Fabry disease standard operating procedures. A cost-utility analysis was also included as a secondary analysis.

The comparator of ERT was based on a weighted average of agalsidase alfa (70%) and agalsidase beta (30%). The source of the clinical evidence to support the cost-minimisation analysis was the ATTRACT study where comparable efficacy between migalastat and ERT was demonstrated based on pre-specified criteria.[2]

The analysis covered a 26-year time horizon and included the medicine acquisition costs of migalastat, agalsidase alfa and agalsidase beta (ERT) and the administration costs of ERT. The cost of ERT was estimated assuming a patient weight of 78.66kg based on the Scottish Health Survey.[11] Patients in the ATTRACT study had an average weight of 74.1kg and this weight was used in the sensitivity analysis. In terms of ERT administration costs, it was assumed that patients receive ERT infusions in an outpatient setting for the first 3 months of treatment followed by homecare infusions from month 3 onwards. Homecare resources included delivery of medication and disposables, nurse time to administer medication to 50% of patients (informal carers assumed to support the administration of treatment for other patients) and the cost of pre-infusion medications to reduce impact of infusion reactions. In the base case analysis, the company used an NHS perspective, as appropriate. However, the company also highlighted that patients and carers often incur additional costs due to productivity losses related to ERT infusions. To capture these other costs, the company provided a sensitivity analysis which used a societal perspective.

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as being acceptable for implementation in NHS Scotland. Under the PAS a simple discount was offered on the list price. Without the PAS, the company estimated an incremental cost of £1,157,518 with migalastat. With the PAS, migalastat became a cost-effective treatment option, providing health benefits at a lower overall cost than ERT.

In a sensitivity analysis, the costs of productivity losses due to ERT infusions were included based on an average UK wage of £15.27 per hour and assuming 59% of patients are employed.[12] It was also assumed that 2 hours of work would be lost per infusion for both the patient and the carer, with 50% of patients assumed to have a carer. This resulted in an annual productivity loss of £468 per patient and £580 per carer (as a higher proportion of carers are assumed to be in employment).

The following limitations were noted:

- The results are particularly sensitive to the weight of patients in the model. The base case analysis used a higher weight than the study in order to reflect the Scottish population (78.66kg vs 74.1kg). However, initial responses from SMC clinical experts indicate patients with Fabry disease have a similar weight to the general population.

- Clinical study data indicate comparable efficacy between migalastat and ERT, though there is some uncertainty about this conclusion due to small patient numbers, lack of non-inferiority study design, and lack of longer term data. However, there is also a suggestion in some of the secondary endpoints of potential improved outcomes in the migalastat arm. Overall, the assumption of comparable efficacy seems reasonable.

Despite these limitations, the economic case has been demonstrated as with the PAS migalastat provides health benefits at a lower overall cost than ERT.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from The MPS Society.

- The MPS Society has received 18% pharmaceutical company funding in the past two years, but none from the submitting company.

- Fabry disease is an inherited lysosomal storage disease, which can lead to a wide range of debilitating symptoms. Its effects are variable with some people showing progressive disease and others displaying only minor symptoms. Depression and psychological problems including low mood and fatigue can impact the ability to cope on a day to day basis.

- Current treatment is with Enzyme Replacement Therapy (ERT). ERT is given as an intravenous infusion every two weeks, initially in hospital, then by homecare nurses in the home. A small number of patients self-infuse, or rely on carers who are trained to administer the infusion. This impacts work, social plans, holidays, and having to deal with storage issues. ERT can have a positive impact on symptom control and quality of life.

- Migalastat is a comparable treatment to ERT, for those with an amenable mutation. It is an oral therapy, which is self administered. This would positively impact quality of life and reduce the time taken off work or education.

Additional information: guidelines and protocols

The National Specialist Commissioning Team requested prescribing physicians prepare the UK Adult Fabry Disease Standard Operating Procedures in 2012. These contain starting criteria for ERT: in males with classic mutations (leucocyte enzyme activity <1%) ERT should commence at diagnosis; in females and those males with later onset mutations with higher levels of leucocyte enzyme activity, ERT should commence when patients experience uncontrolled pain, evidence of renal, cardiac or neurovascular disease, or gastrointestinal symptoms that significantly reduce quality of life.[6]

The European Fabry Working Group published a consensus document in 2015: Recommendations for initiation and cessation of ERT in patients with Fabry disease.[4] For male patients' ≥16 years old with classic Fabry disease, treatment should commence on diagnosis. Female patients with classic disease and male patients with non-classic disease should commence treatment when there are early clinical signs of kidney, heart or brain involvement. Female patients with non-classic disease may be considered for treatment if there are early clinical signs that are considered to be caused by Fabry disease.

Additional information: comparators

ERT: agalsidase alfa or agalsidase beta.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Migalastat	**123mg orally once every other day**	**210,000**
Agalsidase alfa	0.2mg/kg by IV infusion every other week	111,139
Agalsidase beta	1mg/kg by IV infusion every other week	114,223

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eMC Dictionary of Medicines and Devices browser on 13 July 2016 except migalastat from the company submission. Costs based on a body weight of 70kg. IV: intravenous. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

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11. The Scottish Government. Scottish Health Survey - 2014 - Supplementary Table 13 [Obesity]. 2015.
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This assessment is based on data submitted by the applicant company up to and including 13 September 2016.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.