Committee, projector and public slides

Migalastat for treating Fabry disease

Highly Specialised Technologies Evaluation Committee

Second meeting, 22 November 2016

Chair: Peter Jackson

Company: Amicus Therapeutics

Fabry disease

- X-linked lysosomal storage disease caused by non-functioning or reduced activity of enzyme alpha-gal A
- Accumulation of substrates Gb3 and lyso-GB3 in tissues leading to irreversible, progressive organ damage
  - Kidney disease, heart disease and stroke
- Symptoms include pain, fatigue, gastrointestinal problems, headaches, impaired sweating, vertigo and hearing loss
- Reduces health-related quality of life and life expectancy
- Approximately 142 people eligible for treatment

Current management

- Currently no cure for Fabry disease
- The current treatments are enzyme replacement therapies (ERT), agalsidase alfa and agalsidase beta
  - Replace the non-functioning enzyme
  - Help prevent the development of symptoms and slow disease progression
- Administered by infusion every 2 weeks, usually at home
- Estimated cost per month, at list price (depending on age and gender):
  - Agalsidase alfa £8,292 – £12,483
  - Agalsidase beta £7,928 – £10,968
  - *Confidential discounts agreed by national tender; not reported here*
- ERT has not been evaluated by NICE

Migalastat (Galafold)

- Binds to α-gal A as it is being made, helping it to fold correctly and improve its function
- Indicated for people with Fabry disease who have amenable mutations
  - Amenability tested at diagnosis, by comparing results from standard genetic test to list of amenable mutations
- Administered orally, every other day
- Cost per month, at list price: £16,153.85
  - Patient Access Scheme discount agreed with Department of Health; not reported here

Committee considerations

- Fabry disease is a serious disease that limits life expectancy
- ERT is a treatment option but there are unmet needs regarding the administration
- Some limitations to the evidence, migalastat may provide similar clinical benefits to ERT with the advantages of oral administration
  - Preliminary recommendations encourage more research
- The economic model submitted by the company was reasonable
- Some uncertainties in the model (e.g. the disutility for infusion administration) but results showed that migalastat can provide additional health benefits
- With all discounts considered, the cost of migalastat is lower than that of ERT

ECD preliminary recommendations

1.1 The case for national commissioning of migalastat is supported when used within its marketing authorisation, as an option for treating Fabry disease in people over 16 with amenable mutations. With the discount agreed in the patient access scheme, migalastat provides health benefits at a lower cost than enzyme replacement therapy (ERT) at its current price.

1.2 The committee noted that there were important limitations and uncertainties in the evidence presented for migalastat, and that NICE has not evaluated ERT (agalsidase alfa and agalsidase beta) for treating Fabry disease. It encourages the company, NHS England and treatment centres to collect more evidence, particularly on the longer-term benefits of migalastat and ERT for treating Fabry disease, which should inform a future evaluation of the costs and benefits of treatment options for Fabry disease.

Comments on ECD consultation

Consultees

- Amicus Therapeutics
- MPS Society
- NHS England

Commentators

- Shire

Department of Health stated that it had no comments

Comments on ECD: Amicus Therapeutics (1)

- All relevant evidence has been taken into account
- In general agrees with ERG's overall interpretations
- Recommendations are sound and suitable basis for guidance
- Committee's conclusion on infusion-related disutility was inconsistent with eliglustat evaluation
  - Committee considered ERG's estimates (-0.018) more likely than company estimate (-0.05)
  - In eliglustat discussion, committee appeared to prefer utility gain of 0.05 for oral treatment

Comments on ECD: Amicus Therapeutics (2)

- Requested clarification and corrections of evidence in PMB and ECD:
  - **ECD Section 4.7:** report the 18-month statistically significant decrease in LVMi from baseline for people switching to migalastat vs no significant change in baseline for people remaining on ERT in the ATTRACT trial
  - **ECD Section 5.2:** company noted that reduced doses of agalsidase beta are not licensed
  - **PMB Page 21:** clarify that none of the imbalances in baseline characteristics of people in the ATTRACT trial were not statistically significant. Report further GFR data in the ATTRACT OLE

Comments on ECD: MPS Society

- Welcomes the recommendation of migalastat within its marketing authorisation
- Clinical and patient views validated opinion that migalastat is comparable to ERT and may improve autonomy and quality of life due to oral administration
- Supports recommendation that more data should be collected on migalastat and ERT

Comments on ECD: NHS England

- Does not believe all relevant evidence has been taken into account
- Cost effectiveness of ERT has not been considered as part of this evaluation
- Evidence suggests that cost per QALY for ERT is very high
- Evaluation of all disease-modifying therapies for Fabry disease is required

Comments on ECD: Shire (1)

- Definition of amenable mutations should be clearer with more explanation of how amenability testing will be monitored
  - Uncertainties about criteria for amenability and the company assay
  - Comparability of ERT and migalastat shown in people with amenable mutations only
- Uncertainties in clinical trial evidence
  - GL-3 inclusions in FACETS were not statistically significant and the EMA considers that GL3 inclusions cannot predict clinical benefit
  - Concerns on non-inferiority conclusion in ATTRACT – appropriate analysis was not done, arbitrary non-inferiority margin and trial population gender imbalance relative to real-world Fabry population
- Note that a 2-hour fasting period is required before and after taking migalastat – follow-up adherence service may be required

Comments on ECD: Shire (2)

- **Section 5.2** Question the impact of limited penetration of ERT in key tissues and what evidence there is to show that migalastat addresses this
  - Uncertainty about how much migalastat increases enzyme delivery to relevant organs
- **Section 5.5** Expert opinion that migalastat is at least as good as ERT is not supported by evidence
- **Section 5.7** Evidence for statement that migalastat might be more beneficial for cardiac complications is weak

Key issues for consideration

- What is the committee's view of the consultation comments received?
  - Amicus
  - MPS Society
  - Shire
  - NHS England
- Do the comments on evidence and uncertainties from Amicus and Shire change the committee's view of migalastat's effectiveness?
- What is the committee's view on the utility gain associated with oral administration?
- Are the preliminary recommendations appropriate given uncertainties in the cost-effectiveness of ERT?
- ***Has the committee seen evidence to change its preliminary recommendations?***