Part 1

Chair's presentation Eliglustat for treating type 1 Gaucher disease

Highly Specialised Technology Evaluation Committee

Second committee meeting

Peter Jackson

16th February 2017

History

Sept 2016	• 1st committee meeting • ECD drafted
Oct 2016	• Company advises of revised list price and PAS application • ECD on hold
Nov/Dec 2016	• Company submits analyses based on updated prices and also revised patient number estimates • ERG prepares critique
Feb 2017	• 2nd committee meeting

Gaucher's disease

- Gaucher disease
  - Rare, autosomal recessive lysosmal storage disorder
  - Deficiency of an enzyme (glucocerebrosidase)
    - Storage of complex lipids
    - Gaucher cells – liver, spleen, bone marrow, occasionally lungs
  - 3 types
    - Type 1 >90%
      - 1 in 50-100,000 live births
      - 1 in 200,000 in non-Ashkenazi Europeans (250-400)
      - 1 in 500-1000 live births (Ashkenazi family origins)
      - Clinical manifestations: anaemia, thrombocytopenia, splenomegaly, hepatomegaly, bone pain, bone crises, Parkinson's disease.

Current management of Type 1 Gaucher disease (1)

- Enzyme Replacement therapy (IV)
  - Imiglucerase or velaglucerase alfa
    - IV administration every 2 weeks
    - Burdensome and inconvenient for patients/families
    - Infusion related reactions
  - Miglustat
    - When ERT not suitable/ occurrence of immune reactions
    - Modest efficacy
- Supportive therapies
  - Blood products, bisphosphonate therapy, analgesia

Current management of Type 1 Gaucher disease (2)

- No NICE guidance for Gaucher disease
- Lysosomal storage disorder expert advisory group (2012)
  - Recommends velaglucerase
    - 1st choice (based on cost)
    - Imiglucerase efficacy considered equivalent
- NHS England. Manual for prescribed specialised services (Nov 2012)
    - Lists Gaucher disease
    - All 3 drugs commissioned
- Expert consensus guidelines in development

Eliglustat

- Ceramide analogue
- Inhibits enzyme glucosylceramide synthase
  - Reduced production of glucosylceramide (and Gaucher cells)
- Oral, administered twice daily
- Marketing authorisation:
  - Type 1 Gaucher disease in adults who are **CYP2D6** poor (PM), intermediate (IM) or extensive (EM) metabolisers
  - **84mg* twice daily in IM & EM**
  - **84mg* once daily in PM**
- Cost
  - £342.23 for one capsule, confidential patient access scheme discount available

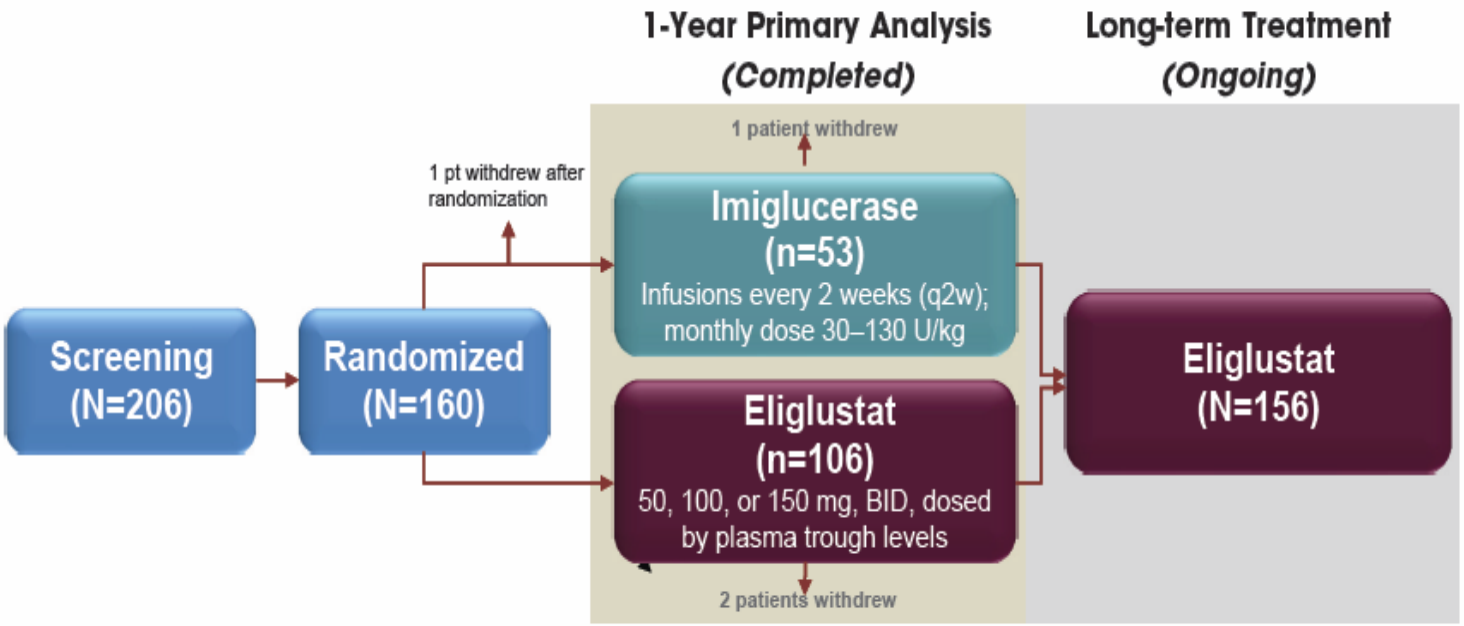
* equivalent to 100mg eliglustat tartrate

Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Adults with type 1 Gaucher disease who are CYP2D6 poor metabolisers, intermediate metabolisers or extensive metabolisers	Adults with Gaucher disease type 1.
Intervention	Eliglustat	Eliglustat 84.4mg (as free base, equivalent to 100mg eliglustat tartrate) twice daily in intermediate metabolisers and extensive metabolisers, and once daily in poor metabolisers.
Comparators	• Imiglucerase • Velaglucerase alfa For people for whom enzyme replacement therapy is unsuitable: • miglustat	• Imiglucerase • Velaglucerase alfa The company stated that miglustat is not considered a relevant comparator as it is only used in a very small proportion of patients in England for whom ERT is unsuitable (<2% [4 patients] in 2015). The company stated that eliglustat would not be expected to be used in place of it
Outcomes	• type 1 Gaucher disease therapeutic goals • mortality • adverse effects of treatment • health-related quality of life (for patients and carers).	As per scope. No data identified to allow the impact on carers to be assessed

ENCORE – trial design

Phase 3, open label, non-inferiority trial



Key Inclusion Criteria	Key Exclusion Criteria	Stratification
• ≥18 years of age • ERT ≥ 3 years • At pre-specified therapeutic goals on ERT	• Cardiac History* • Splenectomy within 3 years • SRT or pharm. chaperone within 6 months	• ERT dose < 35 U/kg/q2w or ≥ 35 U/kg/q2w

*History of coronary artery disease, including myocardial infarction, cardiac ischemia, heart failure; clinically significant arrhythmia or conduction defect.

ERT=-enzyme replacement therapy;
SRT=substrate reduction therapy

Key: BID, twice daily; ERT, enzyme replacement therapy; SRT, substrate reduction therapy.

ENCORE – primary outcome and results

- Primary composite endpoint
  - % patients who remained stable for 52 weeks in all of the following parameters:
    - Haemoglobin levels ↓ ≤1.5g/dL from baseline
    - Platelet counts ↓ ≤25% from baseline
    - Spleen volume ↑ ≤25% from baseline
    - Liver volume ↑ ≤20% from baseline

- Eliglustat
  - 84.8% (95% CI 76.2%-91.3%) met endpoint criteria
- Imiglucerase
  - 93.6% (95% CI 82.5-98.7%) met endpoint criteria

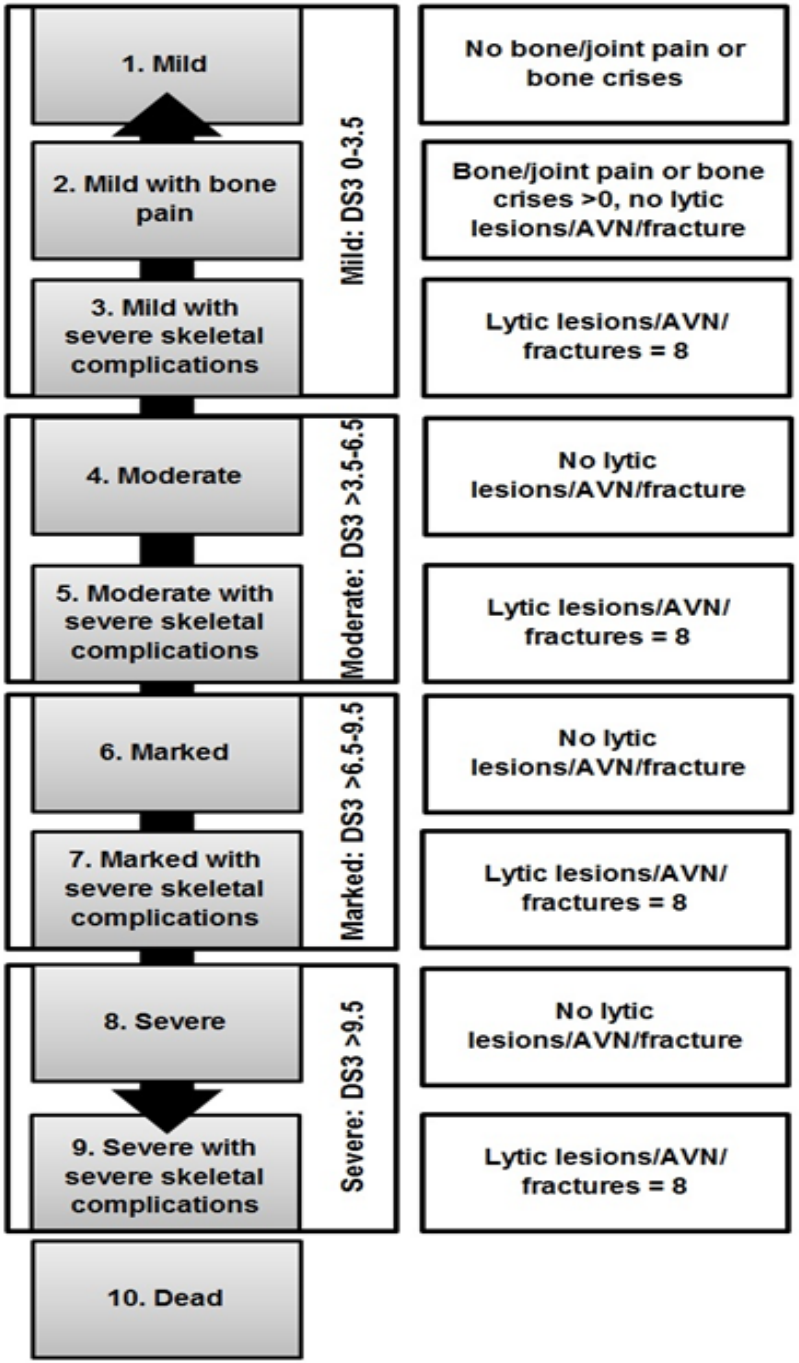
ENGAGE

Double-blind, placebo controlled, phase 3, with open label extension phase

- Treatment naïve population (n=40)
  - n.b. inclusion criteria allowed people who had previous treatment with ERT as long as they were not being treated at time of recruitment to trial
- Week 4 to 39, 50-100mg BD
- Statistically significant and clinically meaningful improvement in spleen volume at 39 weeks
  - mean difference of 30.03% compared with the placebo group (-27.8% eliglustat, 2.3% placebo)
- Statistically significant efficacy on all secondary endpoints

ERG comments

- Few eliglustat data for treatment-naïve patients; no comparative data with ERT
- Trials generally included intermediate and extensive metabolisers
- **Key issue** - The assumed average dose of ERT (42.4 U/KG) taken from ENCORE is much higher than the dose used in clinical practice:
  - Prescribing data: Average dose of 25 U/kg in England
  - International Gaucher Register: Average dose of 21 U/kg in UK
  - SPCs: 60U/kg every two weeks
  - SOP: maintenance dose of 15-30 U/kg
  - ERG adviser: typical doses were around 25U/kg (range: 15-28 U/kg)
  - Expert submission to NICE: 20-40 U/kg
- ERG highlighted that lower doses of ERT will affect the long-term costs in the model



Model Structure

- 10 state Semi-Markov model comparing eliglustat with imiglucerase and velaglucerase
- States defined by DS3 severity scoring system (a validated measure of disease severity)
- 2 populations: stable ERT and treatment-naïve
- Metaboliser status considered as subgroups
- Time horizon 70 years
- Cycle length 1 year
- Costs and benefits discounted at 3.5%

Assumptions

- Transition probabilities:
  - Stable ERT population: differential clinical effectiveness assumed in the 1st year (based on ENCORE) and then equal effectiveness in subsequent years (based on DS3 score study)
  - Treatment naïve population: effectiveness assumed equal and based on eliglustat arm of ENGAGE
- Discontinuation: rate of 1.9%
  - For both eliglustat and ERT in treatment-naïve population
  - For eliglustat only in stable ERT group
- Outcomes at 39 weeks from ENGAGE used for people at 1 year in model
- Mortality – same for all treatments and health states
- Differential monitoring and management costs applied to each health state, broadly increasing with severity of disease.
- No costs associated with adverse events included
- Neither eliglustat nor the comparators required additional training of healthcare staff
- No administration costs included for eliglustat

Company's base case results based on list prices (updated for eliglustat)

Eliglustat vs. imiglucerase		
	Incremental QALYs	Incremental Cost
ERT stable IM/EM	2.28	£687,837
ERT stable PM	2.28	-£1,698,539
ERT naïve IM/EM	2.43	£672,251
ERT naïve PM	2.43	-£1,855,035

Eliglustat vs. velaglucerase		
ERT stable IM/EM	2.28	-£519,226
ERT stable PM	2.28	-£2,905,602
ERT naïve IM/EM	2.45	-£467,818
ERT naïve PM	2.45	-£2,995,104

Note – results based on eliglustat PAS and confidential discounts for ERT presented in part 2

ERG exploratory analyses

- Additional administration costs for eliglustat (£14.40 monthly dispensary cost)
- Revised administration costs for ERT (Home therapy cost equal to hospital cost rather than higher);
- Revised estimate of utility benefits of oral therapy (Estimate of ‘0.05’);
- Revised modelling of mortality to allow for increased mortality risk for marked and severe patients;
- Reduction in dose of ERT in line with UK practice (25 units per kilogram);
- Using ENCORE effectiveness data in the treatment naïve population during the first cycle

ERG base case results based on updated list price for eliglustat

Eliglustat vs. imiglucerase		
	Incremental QALYs	Incremental Cost
ERT stable IM/EM	1.05	£2,638,293
ERT stable PM	1.05	-£6,825
ERT naïve IM/EM	1.04	£2,605,712
ERT naïve PM	1.04	-£49,688
Eliglustat vs. velaglucerase		
ERT stable IM/EM	1.05	£1,849,412
ERT stable PM	1.05	-£795,706
ERT naïve IM/EM	1.06	£1,900,060
ERT naïve PM	1.06	-£755,340

Key drivers remain:

Costs – ERT dose

QALYs – Utility increment

Company budget impact analysis (1)

- 5 year budget impact model estimating costs to NHS
- Based on estimates of total costs generated cost consequence model
- Newly diagnosed patients are assumed to start treatment on eliglustat rather than imiglucerase/velaglucerase
- Costs based on the licensed dose of eliglustat and the dosing of ERTs used in the ENCORE clinical trial
- Effects of mortality and discontinuation are included in the estimated total costs
- Model results for people who are intermediate or extensive metabolisers were used (majority of patients in the trials)
- Testing costs and AE costs were assumed to be [redacted] each year

Company budget impact analysis (2)

- Company has now revised the likely uptake of the eliglustat in the UK, based on experiences in other countries
  - impacts budget impact analysis results only

	2017	2018	2019	2020	2021
Original patient numbers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised patient numbers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Company budget impact results (updated with revised eliglustat list price)

Based on original patient numbers (ERG critique table 4)					
	2017	2018	2019	2020	2021
Total	£184,218	£304,543	£394,177	£493,482	£620,247

Based on revised patient numbers (ERG critique table 9)					
	2017	2018	2019	2020	2021
Total	£84,559	£193,784	£331,078	£442,311	£571,487

ERG exploratory analyses – budget impact

The ERG explored the impact of:

- All the assumptions explored in cost-consequence model (see slide 15)
- Zero mortality
  - Including mortality means that total costs of treating patients represents the average over a lifetime, not the cost of treating one patient for 5 years, thereby underestimating costs
- No treatment discontinuation
- Additionally, patient numbers based on:
  - Company's base case estimates
  - Company's revised estimates

ERG budget impact results (updated with revised eliglustat list price)

Based on original patient numbers					
	2017	2018	2019	2020	2021
Total	£5,058,551	£8,172,429	£10,130,622	£12,088,535	£14,048,638

Based on revised patient numbers					
	2017	2018	2019	2020	2021
Total	£2,321,945	£5,058,377	£7,688,503	£9,682,106	£11,677,472

Additional ERG scenario (based on revised eliglustat list price)

- ERG states that assuming population is entirely intermediate and extensive metabolisers overestimates budget impact of due to the lower dose of eliglustat required in the PM population.
- Explores impact of assuming that 4% of eliglustat patients are PM, based on the proportion of PM in the ENGAGE trial.

ERG base case, based on original patient numbers					
	2017	2018	2019	2020	2021
Total	£4,818,908	£7,785,194	£9,650,430	£11,515,367	£13,382,472

ERG base case, based on revised patient numbers					
	2017	2018	2019	2020	2021
Total	£2,211,946	£4,818,731	£7,324,191	£9,223,107	£11,123,765

Expert comments

- Revised patient numbers:
  - Company's revised estimates in year 1 and 2 potentially too low, but overall the forecast of [redacted] patients was realistic
  - NHS England stated that initial uptake may be between 30-40 patients, thereafter rising to between 60-90 patients.

- NHS England stated that ERT is used more cost effectively in Gaucher than in Fabry disease because:
  - Gaucher disease is more acute so effectiveness of ERT is more obvious
  - Clinicians are able to dose titrate ERT, using the lowest dose which effectively controls disease – not possible in Fabry disease
  - More patients receive ERT for Fabry disease (>400) than for Gaucher disease (~ 250)

Issues for discussion

- Are the revised patient number estimates reflective of clinical practice in England?
- Are the ERG scenarios assuming that 4% of eliglustat patients are poor metabolisers preferred?