Chair’s presentation
Dinutuximab beta for neuroblastoma [ID910]

3rd Appraisal Committee meeting
Committee D
Lead team: William Turner, Peter Hall and Malcolm Oswald
ERG: BMJ-TAG; NICE Decision Support Unit
NICE technical team: Anna Brett, Nwamaka Umeweni
Company: EUSA Pharma
12 June 2018
Key issues for discussion

- Do any of the responses to the consultation change the committee’s conclusions?
  - Most appropriate data for the comparator treatment:
    - ANBL0032 trial (Yu et al. 2014);
    - SIOPEN HR-NBL-1 trial?
  - Clinical plausibility of Gompertz extrapolation for event-free survival
  - Appropriateness of modelling a discontinuation rate:
    - Discontinuation due to toxicity – dinutuximab without IL-2;
    - Discontinuation due to toxicity – dinutuximab with/without IL-2;
    - Proportion of patients treated per cycle (dinutuximab without IL-2)
- Impact of proposed patient access scheme on cost-effectiveness
- Cancer Drugs Fund proposal
## Dinutuximab beta (Qarziba, EUSA)

| Marketing authorisation granted May 2017 under exceptional circumstances | • Treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by MAT and SCT, as well as patients with a history of relapsed or refractory neuroblastoma, with or without residual disease  
• In patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first line therapy, dinutuximab beta should be combined with IL-2 |
| Mechanism of action | Immunotherapy – a monoclonal, chimeric antibody that targets GD2, a glycolipid in neuroblastoma cells |
| Administration | Intravenous infusion |
| Dosing frequency | Continuous infusion over the first 10 days of each course at the daily dose of 10 mg/m² |
| List price excluding VAT | Acquisition cost: £7,610 per vial; average cost of a course of treatment: £152,200 |
| PAS | Company has applied for a simple discount PAS |

MAT, myeloablative therapy; SCT, stem cell transplant
## Committee’s key conclusions

**ACD: Not recommended**

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
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<tbody>
<tr>
<td><strong>Clinical effectiveness</strong></td>
<td>Matched-adjusted indirect treatment comparison shows dinutuximab beta improves EFS and OS compared with isotretinoin</td>
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<tr>
<td><strong>Cost effectiveness</strong></td>
<td></td>
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<tr>
<td><strong>Comparator data</strong></td>
<td>Most recent data for isotretinoin (Yu. et al. 2014) 12 years’ data so no extrapolation needed</td>
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</tbody>
</table>
| **Extrapolations for dinutuximab** | EFS: 1-knot spline  
OS: Gompertz or 2-knot spline |
| **Cure threshold**              | 10 years preferred; others could be plausible  
Relapses after 5 years rare, but possible |
| **Most plausible ICERs**        | £62,309 - £79,935 per QALY gained (probabilistic estimates)  
ICER sensitive to small changes in survival estimates |
| **Uncertainty**                 | Long-term benefit with dinutuximab |
| **End of life/other factors**   | End of life criteria not met  
Some health-related benefits not captured in model |
| **Cancer Drugs Fund**           | Data collection could help resolve uncertainty but no current plausible potential for cost-effectiveness |
ACD consultation responses

• Consultee comments from:
  – EUSA Pharma

• Commentator comments from:
  – Dr Juliet Gray (clinical expert)
  – Nick Bird (patient expert)

• Web comments from:
  – 3 Parents/Carers
  – 3 NHS Professionals
Comments from parents, carers, NHS professionals

• Dinutuximab beta is standard care in Europe and North America; children in UK should not be disadvantaged
• Preliminary recommendation could lead to inequity for children; some families will fund treatment while others unable to do so
• Clinical benefit is clear; further randomised study unacceptable
• Dinutuximab beta is well tolerated (and subtly different from dinutuximab alpha)
• Agree to focus on high risk group and using long-term isotretinoin data in model
• Potential gain in terms of young lives saved is high, and the proportional benefit of extending a child’s life compared to an adult’s should be considered
• Urge compromise to negotiate a price for CDF recommendation
• More data collection may show dinutuximab beta as even more effective; clinical investigations will carry on elsewhere; important for UK clinicians to be involved
• Small patient numbers; will have little impact on NHS budgets
• Difficulties of undertaking research in rare diseases should be recognised
• Companies need to remain incentivised to develop treatments for rare diseases
• Assessment by Highly Specialised Technology process may be more appropriate
Additional comments from clinical and patient expert

Clinical expert

- Relapsed/refractory population conclusions will not apply should dinutuximab beta not be recommended, because patients will not receive it for initial treatment
  - Patients who have previously received dinutuximab should only receive it again as part of a clinical trial (currently 2 trials for this group)
- Challenges of obtaining robust data in rare population of children:
  - European Neuroblastoma Research Group decided it unacceptable to include control arm in studies because of benefit shown with dinutuximab
  - As anti-GD2 therapy is now standard care it would not be feasible to run a further randomised study to assess long-term benefits
  - Efficacy assessments will be based on comparison with historical controls

Patient expert

- Isotretinoin arm of ANBL0032 does not represent most appropriate control arm; better comparator would be BuMel arm of SIOPEN R1 randomisation (more detail later)
Company’s comments
Issues with STA process

• Using STA to appraise treatments for very rare disease in paediatric population
  – Does not allow for uncertainties in valuing potentially curative treatments
  – Likely to produce negative recommendation for orphan drugs
  – Discriminates against children with rare disease

• QALY approach does not fully capture value
  – Difficulty in understanding and valuing children’s health-related quality of life
  – Parental burden (ability to work); societal perspective should be considered

• More flexibility needed for rare, paediatric diseases outside HST programme

• Preliminary recommendation likely amounts to breach of a child’s right of access to highest attainable standard of health and facilities for the treatment of illness

STA, Single Technology Appraisal; QALY, quality-adjusted life year; HRQOL, health-related quality of life; HST, Highly Specialised Technologies
Company’s comments
Clinical evidence

- Difficulties of conducting clinical trials in orphan disease areas should be acknowledged and taken into account
- Patient numbers will always be small
- APN311-302 trial had no control arm because it was deemed unethical to treat patients without immunotherapy
- Trial designed and executed by clinicians to inform clinical practice
- Immature data because treatment was made available to patients as soon as possible
- APN311-302 represents the best available evidence:
  - Length of follow-up data is considerable
  - May be more reflective of clinical practice than a randomised controlled trial
- Waiting for certainty on long-term outcomes is not realistic
Company’s comments
Relapsed/refractory population

- ACD considered evidence for relapsed/refractory population not relevant to current NHS practice because in practice these patients will have already had dinutuximab beta.
- Evidence is relevant because although current patients have had dinutuximab beta through the clinical trial, future patients may not.
- Additionally, not all patients will have initial treatment with dinutuximab beta and so could be eligible after relapse.
- Inconsistencies in ACD conclusions:
  - In clinical practice almost all relapsed/refractory patients have had dinutuximab beta.
  - Dinutuximab beta cannot be considered established clinical practice because it is only given in a trial.
- Committee view on relapsed/refractory patients having access to dinutuximab beta outside of clinical trials and in future clinical practice would be welcome.
Company’s comments
End of life

Application of end of life criteria
• 2 year life expectancy threshold arbitrary and biased against children
• End of life criteria based on data from adults and does not apply to paediatric populations

End of life care costs
• Experts advised that for uncontrolled disease patients may receive more intensive palliative care than that modelled in the failure health state
• DSU commented that because all modelled patients die, the impact of including the costs of this would be negligible
• Company note however that not all modelled patients die due because of the disease
• Company consider that including these costs would further decrease the ICER and ask committee to take this into consideration
Company’s new evidence
EFS extrapolation for dinutuximab beta

Company suggest Gompertz best reflects the expected plateau after 5 years (i.e. no/very few events after 5 years)
Company’s new evidence
EFS extrapolation: Goodness-of-fit (AIC criteria)

Committee’s preferred (spline k=1 scale=odds)
Company’s proposal (Gompertz)

DSU corrected small error and reproduced diagram
Monthly risk of progression

**Gompertz**: <0.10% after 5 years; <0.02% after 7.4 years

**Spline**: >0.10% for years 5-10

Which is most clinically plausible?
Company’s new evidence
Discontinuation rate

- Modelled cost-effectiveness assumed patients had 5 cycles of treatment at the full dose
- However, in practice, dose reduction or permanent discontinuation occurs with toxicity
- Discontinuation rates from the trial have been applied to the model and revised cost-effectiveness analysis presented

<table>
<thead>
<tr>
<th>APN311-302 trial</th>
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<tbody>
<tr>
<td>Discontinuation due to toxicity or tolerability</td>
</tr>
<tr>
<td>Dinutuximab beta + isotretinoin (no IL-2)</td>
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<tr>
<td>Dinutuximab beta + isotretinoin +/- IL-2</td>
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Company’s new analysis
Cost-effectiveness results (list price)

<table>
<thead>
<tr>
<th></th>
<th>EFS: spline OS: Gompertz</th>
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<th>EFS: Gompertz OS: Gompertz</th>
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<tr>
<td><strong>10 year cure point</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No discontinuation rate</td>
<td>£75,831</td>
<td>£87,164</td>
<td>£62,886</td>
</tr>
<tr>
<td>% discontinuation rate</td>
<td>£72,587</td>
<td>£83,450</td>
<td>£60,128</td>
</tr>
<tr>
<td>% discontinuation rate</td>
<td>£71,837</td>
<td>£82,592</td>
<td>£59,491</td>
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<td><strong>5 year cure point</strong></td>
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<td>No discontinuation rate</td>
<td>£60,824</td>
<td>£61,222</td>
<td>£58,651</td>
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<tr>
<td>% discontinuation rate</td>
<td>£58,227</td>
<td>£57,686</td>
<td>£56,082</td>
</tr>
<tr>
<td>% discontinuation rate</td>
<td>£57,627</td>
<td>£57,096</td>
<td>£55,489</td>
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Most plausible ICER range using committee’s preferred assumptions in ACD highlighted
DSU’s critique
Discontinuation rate

- Company’s approach may double-count patients discontinuing due to toxicity and then progressing (more than 1 reason recorded for treatment discontinuation) and therefore underestimate time on treatment
- More accurate to use proportion of patients treated per cycle
- Discontinuation rate from arm without IL-2 most accurate because model assumes 0% patients have IL-2

Comparison of different approaches to discontinuation: proportion of patients treated per cycle

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Previous approach: EFS spline</th>
<th>Previous approach: EFS gompertz</th>
<th>Company’s new approach: gompertz</th>
<th>DSU approach: Patients treated per cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100.0%</td>
<td>100.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>99.4%</td>
<td>96.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>97.5%</td>
<td>94.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>94.6%</td>
<td>91.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>91.5%</td>
<td>89.0%</td>
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# DSU’s analysis

## Cost-effectiveness results (list price)

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<tr>
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<td>No discontinuation rate</td>
<td>£75,831</td>
<td>£87,164</td>
<td>£62,886</td>
<td>£70,757</td>
</tr>
<tr>
<td>DSU’s discontinuation rate</td>
<td>£75,251</td>
<td>£86,500</td>
<td>£63,916</td>
<td>£71,910</td>
</tr>
<tr>
<td><strong>5 year cure point</strong></td>
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<td></td>
<td></td>
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<tr>
<td>No discontinuation rate</td>
<td>£60,824</td>
<td>£60,239</td>
<td>£58,651</td>
<td>£58,109</td>
</tr>
<tr>
<td>DSU’s discontinuation rate</td>
<td>£60,359</td>
<td>£59,782</td>
<td>£59,611</td>
<td>£59,052</td>
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Comparator data
Patient expert comments

• Isotretinoin arm of ANBL0032 does not represent most appropriate control arm
• Company’s original submission included a naïve comparison with a historical control from SIOPEN HR-NBL1 high-risk neuroblastoma trial
• Trial included patients who had BuMel and CEM consolidation therapy whereas majority of patients having dinutuximab beta would have had BuMel
• Company was directed to instead use the isotretinoin arm from the Children’s Oncology Group (COG) ANBL0032 trial
• However, specific components of treatment differ between the SIOPEN and COG trials and could lead to confounding:
  – Different induction therapies; procedures performed at different time-points
  – Consolidation therapy in COG trial would have been CEM not BuMel
  – Patients could enrol on any protocol prior to ANBL0032
• Better comparator would be BuMel arm of SIOPEN R1 randomisation
  – Published results with up to 5 years of follow-up
  – 29/296 patients had dinutuximab; remainder had isotretinoin alone

BuMel, busulfan + melphalan hydrochloride; CEM, carboplatin, etoposide + melphalan
Comparator data

DSU comments

• In Yu et al. 2014 (isotretinoin data) all patients had CEM consolidation therapy, while most in APN311-302 (dinutuximab beta trial) had BuMel

• BuMel is better than CEM and standard care in UK

• MAIC could not be adjusted for previous consolidation therapy because:
  – lack of population overlap
  – small sample size
  – adjusting would mean assuming all patients had CEM which is not standard practice
  – assumptions were needed about relative effect of dinutuximab beta following different consolidation therapies

• Direction or size of the potential bias therefore cannot be determined: It is not known if dinutuximab beta after BuMel is more effective than dinutuximab beta after CEM, or vice versa

• SIOPEN HR-NBL1 R1 randomisation represents an earlier stage in the treatment pathway and so the population is not comparable to the APN311-302 trial

BuMel, busulfan + melphalan hydrochloride; CEM, carboplatin, etoposide + melphalan
Key issues for discussion

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