NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Dinutuximab beta for treating neuroblastoma

1 Recommendations

1.1 Dinutuximab beta is recommended as an option for treating high-risk neuroblastoma in people aged 12 months and over whose disease has at least partially responded to induction chemotherapy, followed by myeloablative therapy and stem cell transplant , only if:

- they have not already had anti-GD2 immunotherapy and
- the company provides dinutuximab beta according to the commercial arrangement (see section 2).

1.2 This recommendation is not intended to affect treatment with dinutuximab beta that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For a child or young person, this decision should be made jointly by them or their parents or carers and their clinician.

Why the committee made these recommendations

Neuroblastoma mainly affects children and young people. Treatments for high-risk neuroblastoma include chemotherapy, radiotherapy, stem cell transplant, surgery and isotretinoin. Dinutuximab beta is an important, potentially curative option for maintenance treatment of the disease.

An indirect comparison with isotretinoin suggests that dinutuximab beta increases survival and the length of time before the disease progresses, compared with current treatment.

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Dinutuximab beta does not meet NICE's criteria for a life-extending treatment at the end of life. Also, the range of cost-effectiveness estimates presented is higher than what NICE usually considers a cost-effective use of NHS resources. But taking into account the uncaptured health-related benefits, the rarity and severity of the disease and the potential lifetime benefit for children with neuroblastoma, dinutuximab beta can be recommended for high-risk neuroblastoma.

Dinutuximab beta also has a marketing authorisation to treat relapsed or refractory disease. This indication was not considered in this appraisal as it is not relevant to current NHS practice; most people with relapsed or refractory disease have already had dinutuximab beta.

2 Information about dinutuximab beta

Marketing authorisation indication	Dinutuximab beta (Qarziba, EUSA Pharma) has a marketing authorisation 'for the 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 myeloablative therapy and stem cell transplantation, as well as patients with a history of relapsed or refractory neuroblastoma, with or without residual disease. Prior to the treatment of relapsed neuroblastoma, any actively progressing disease should be stabilised by other suitable measures. In patients with a history of relapsed or refractory disease and in patients who have not achieved a complete response after first line therapy, dinutuximab beta should be combined with interleukin-2 (IL-2).' The marketing authorisation was granted under 'exceptional circumstances'. This happens when the applicant can show that they are unable to provide comprehensive data on the efficacy and safety of the drug for which authorisation is being sought, because of the rarity of the condition it is intended for, limited scientific knowledge in the area concerned, or ethical considerations involved in the collection of such data.
Dosage in the marketing authorisation	There are 2 modes of administration: • continuous intravenous infusion over the first 10 days of each course at a daily dose of 10 mg/m^2 or

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	• 5 daily infusions of 20 mg/m^2 administered over 8 hours, on the first 5 days of each course. When IL-2 is combined with dinutuximab beta, it should be administered as subcutaneous injections of 6×10^6 IU/m^2/day, for 2 periods of 5 consecutive days, resulting in an overall dose of 60×10^6 IU/m^2 per course. The first 5-day course should start 7 days before the first infusion of dinutuximab beta and the second 5-day course should start at the same time as dinutuximab beta infusion (days 1 to 5 of each dinutuximab beta course). The individual dose is determined based on the body surface area and should be a total of 100 mg/m^2 per course. Based on the severity of adverse drug reactions to dinutuximab beta, patients may have a dose reduction of 50% or a temporary interruption of the infusion. As a result, either the infusion period is prolonged or, if tolerated, the infusion rate may be increased up to 3 mL/h (continuous infusion), in order to administer the total dose.
Price	The dinutuximab beta list price is £7,610 per vial (excluding VAT; company submission). The average cost of a course of treatment (body surface area of 0.63 m^2 and age 3) is £152,200. The company has a commercial arrangement (simple discount patient access scheme). This makes dinutuximab beta available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee (section 6) considered evidence submitted by EUSA Pharma and a review of this submission by the evidence review group (ERG). It also considered additional company analyses and a review of these by the NICE decision support unit (DSU). See the committee papers for full details of the evidence.

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The condition

Dinutuximab beta is an important potential option for high-risk and relapsed or refractory neuroblastoma

3.1 Neuroblastoma mainly affects children and young people. The patient experts stated that high-risk and relapsed or refractory neuroblastoma has a significant effect on children and young people and their families and carers. Children and young people with the condition have anxiety about their illness and treatment as well as discomfort and pain from the disease. The existing treatments and procedures for neuroblastoma are painful and debilitating, with severe and long-lasting side effects (including hearing loss, organ dysfunction, sterility, lack of growth, early onset of puberty, permanent disability, and secondary malignancies). The clinical and patient experts stated that a child's death has a significant effect on family members. The committee noted that treatment can involve many hospital visits and stays causing disruption to school, work and family life. It understood that parents and carers also have anxiety, emotional distress and disruption to their working life and income as well as strain on their relationships. The committee recognised that high-risk and relapsed or refractory neuroblastoma places a significant burden on patients, their families and carers. It concluded that new, effective treatment options would be welcomed.

Current treatments

Isotretinoin is the relevant comparator for decision-making for the maintenance treatment of high-risk neuroblastoma

3.2 The clinical and patient experts explained that the main aim of treatment is to extend event-free survival, but that ultimately a cure is needed. The committee acknowledged that since 2009 almost all patients with high-risk neuroblastoma in England, whose disease has at least partially responded to induction chemotherapy followed by myeloablative therapy and stem cell transplant, were enrolled in the immunotherapy phase of the

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HR-NBL-1 trial (APN311-302; comparing dinutuximab beta plus isotretinoin with dinutuximab beta plus isotretinoin plus interleukin-2). The committee agreed that dinutuximab beta cannot be considered established NHS practice because it has only been used in research as part of a clinical trial and is not routinely commissioned. The committee understood that before dinutuximab beta was available in the trial, maintenance therapy with isotretinoin was considered standard care in the NHS for high-risk neuroblastoma. It concluded that isotretinoin is the relevant comparator for the maintenance treatment of high-risk neuroblastoma that has at least partially responded to induction chemotherapy, followed by myeloablative therapy and stem cell transplant.

Most patients with relapsed or refractory neuroblastoma have already had dinutuximab beta in the clinical trial

3.3 The clinical experts explained that there is no defined treatment pathway for relapsed or refractory neuroblastoma, but treatment is usually chemotherapy, radiotherapy and surgery. They also explained that patients with relapsed or refractory neuroblastoma have a poor long-term prognosis, especially if they have relapsed after treatment for high-risk disease. The clinical experts explained that since 2009 in England almost all patients with relapsed or refractory neuroblastoma have had first-line maintenance treatment with dinutuximab beta in the APN311-302 trial (see section 3.2). A small number of patients with relapsed or refractory neuroblastoma may not have already had dinutuximab beta if they were initially diagnosed as having low or intermediate-risk disease. However, if their disease relapsed or became refractory to treatment, these patients would be considered as having high-risk neuroblastoma. The committee concluded that almost all patients with relapsed or refractory neuroblastoma in clinical practice have already had dinutuximab beta in APN311-302.

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Clinical trial evidence

APN311-302 is the best available evidence, but does not address dinutuximab beta's relative effectiveness compared with isotretinoin

3.4 The clinical evidence for the population with high-risk neuroblastoma came from APN311-302, an open-label phase 3 trial comparing dinutuximab beta plus isotretinoin (n=189) with dinutuximab beta plus isotretinoin plus interleukin-2 (n=190). The primary outcome in the trial was event-free survival at 3 years, with overall survival, overall response, incidence of relapsed or refractory disease and safety as secondary outcomes. The committee acknowledged that 55.4% of people randomised to dinutuximab beta and isotretinoin without interleukin-2 had not had an event at 3 years compared with 61.2% in the group having interleukin-2. This difference was not statistically significant (p=0.3202). For overall survival, 64.1% of people randomised to dinutuximab beta and isotretinoin without interleukin-2 were still alive at 3 years compared with 69.1% in the group having interleukin-2. This difference was not statistically significant (p=0.6114). The committee noted that median event-free and overall survival could not be estimated for either group because the data were immature. The ERG stated that no formal primary cut-off date for the analysis or time period for follow-up was specified for APN311-302. It also noted that because the trial was open label there could be performance bias in the assessment of event-free survival and overall response, but this was unlikely to affect overall survival. The committee acknowledged that the trial results showed that concomitant interleukin-2 did not improve event-free or overall survival, and that despite its limitations, APN311-302 was the best available evidence for dinutuximab beta. The committee concluded that because all patients in the trial had dinutuximab beta, the evidence did not inform the decision problem on the relative effectiveness of dinutuximab beta compared with isotretinoin.

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The clinical effectiveness evidence for the population with relapsed or refractory disease is not relevant to NHS clinical practice

3.5 The evidence for this population came from 2 observational studies of dinutuximab beta with isotretinoin and interleukin-2 in patients with relapsed or refractory disease after initial therapy: APN311-202 and APN311-303. The clinical experts explained that people in the NHS with high-risk neuroblastoma who have relapsed disease are likely to have had dinutuximab beta as part of their first-line maintenance therapy in the clinical trial (see section 3.3). The committee noted that none of the patients in APN311-202 and APN311-303 had already had dinutuximab beta. The company explained that it did not support retreatment with dinutuximab beta in the relapsed or refractory population. The clinical experts also explained that the small number of people with low or intermediate-risk disease who may not have already had dinutuximab beta would be considered as having high-risk neuroblastoma if the disease relapsed or became refractory to treatment (and in line with the recommendations in section 1.1. would be eligible for treatment). The committee recognised that the marketing authorisation included patients with relapsed or refractory disease, which could include a very small number of people with low or intermediate-risk disease that has relapsed but is not then considered high-risk. However, it had not seen any evidence for this small subgroup because the evidence for the relapsed and refractory population was not presented by category of initial risk. The committee agreed that the populations in APN311-202 and APN311-303 did not represent the population with relapsed or refractory disease in NHS clinical practice. This was because in England, these patients would be either considered high-risk and have already had dinutuximab beta or would be considered high-risk if their disease had relapsed or become refractory to treatment. It acknowledged that a potential small subgroup of patients with relapsed or refractory disease that was not considered high-risk was not the focus of the appraisal because no cost-effectiveness evidence was presented for this group. Therefore, the committee concluded, with agreement from the company and the experts, that the

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relapsed or refractory population would not be considered further in this appraisal.

Concomitant interleukin-2

Standard NHS practice does not include concomitant interleukin-2

3.6 The committee discussed whether interleukin-2 would be used in NHS practice in line with the dinutuximab beta marketing authorisation. This states that dinutuximab beta should be combined with interleukin-2 when induction therapy does not achieve a complete response. Clinical experts explained that adding interleukin-2 increases toxicity but does not appear to improve efficacy. The patient experts stated that a less toxic treatment allows patients to leave hospital sooner, which is important. The clinical experts explained that standard practice since APN311-302 finished recruiting is not to offer interleukin-2, even when there is residual disease. This is supported by the International Collaboration for Neuroblastoma Research and the UK Children's Cancer and Leukaemia Group and followed by paediatric oncologists in the NHS. In practice further lines of chemotherapy are often used to reduce the need for interleukin-2. The committee noted that this is not in line with the marketing authorisation for dinutuximab beta. But it concluded that standard NHS practice does not include concomitant interleukin-2 in most patients.

Adverse effects

Severe adverse effects occur with dinutuximab beta, but happen more frequently in patients also having interleukin-2

3.7 In APN311-302 severe adverse effects occurred more frequently in people having interleukin-2 (46% with interleukin-2 compared with 27% without interleukin-2). This is in line with clinical expert comments that concomitant interleukin-2 increases toxicity (see section 3.6). Of the 238 infections reported, 132 were in people having interleukin-2 and 106 were in people not having interleukin-2. There were more infections of grade 3 and 4 severity in the group having interleukin-2 than in the group

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who were not (exact figures are considered academic-in-confidence by the company). The committee concluded that dinutuximab beta was associated with severe adverse effects but these occurred more frequently in patients also having interleukin-2.

Indirect treatment comparison

A matched-adjusted indirect comparison shows that dinutuximab beta improves event-free and overall survival compared with isotretinoin

3.8 There was no direct evidence comparing dinutuximab beta with isotretinoin. This was because the European Neuroblastoma Research Group considered it unethical to include a control arm in APN311-302 after benefit was shown with dinutuximab alpha in ANBL0032 (a trial of dinutuximab alpha compared with isotretinoin; Yu et al. 2010). In response to the committee's request, the company provided a matched-adjusted indirect comparison using data from ANBL0032. For the dinutuximab beta arm of the analysis, the company pooled data from both arms of APN311-302 because all these patients had dinutuximab beta and there was no statistically significant difference in the event-free or overall survival results (see section 3.4). The matched-adjusted Kaplan–Meier curves for event-free and overall survival in the dinutuximab beta arm were similar to the observed trial data. The results of the analysis for dinutuximab beta compared with isotretinoin were:

- event-free survival at 70 months: hazard ratio (HR) 0.68; 95% confidence interval (CI) 0.62 to 0.8
- overall survival at 70 months: HR 0.63; 95% CI 0.54 to 0.86.

The committee concluded that dinutuximab beta improved event-free and overall survival compared with isotretinoin.

The most recent data from ANBL0032 are the best available comparator data

3.9 The DSU explained that the results of the matched-adjusted indirect comparison should be interpreted with caution because the hazard ratios

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had been generated assuming the data follows an exponential distribution. It considered this unlikely because the estimates of the hazard ratios would vary according to the time interval chosen. It also noted that it was not possible to adjust the analysis to account for previous consolidation therapy. This differed between the 2 trials and was a potential prognostic factor, and therefore may bias the results (although the direction or size of the potential bias was not known). The committee acknowledged consultation comments suggesting that an alternative comparison with an earlier phase of the HR-NBL-1 trial would help address this problem. However, the company did not have access to these data and the clinical experts considered that an alternative indirect treatment comparison would not resolve uncertainty and would be unlikely to produce different results. The DSU further noted that longer-term data were available from ANBL0032 in Yu et al. (2014), which it considered more appropriate to use in the analysis. It reproduced the analysis using the 2014 data. Because the patient population is the same as in the 2010 data, this did not affect the results of the company's analysis (see section 3.8). The committee agreed that the most recent data from ANBL0032 were the most appropriate to use in the indirect comparison and were the best available source of comparator data.

The company's economic model

The structure of the model is appropriate

3.10 The committee noted that the structure of the company's model was appropriate, but that the ERG had carried out a number of corrections. A partitioned survival method was used to model treatment effectiveness, which used the event-free and overall survival data from the matched-adjusted indirect comparison of dinutuximab beta and isotretinoin to determine mortality and disease progression for each cycle. The committee accepted the structure of the company's economic model and the ERG's corrections.

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Modelling clinical effectiveness of isotretinoin

The most recent data for isotretinoin are the most appropriate to use in the model

3.11 In its original model the company used Kaplan–Meier data from APN311-302 and from ANBL0032 (as reported by Yu et al. 2010) up to 70 months and then extrapolated event-free and overall survival over a 10-year period. However, the DSU noted that the longer-term data from ANBL0032 (Yu et al. 2014) included 12 years of isotretinoin data. The DSU considered it more appropriate to use the Kaplan–Meier data from the 2014 analysis for the full 10 years because this would reduce the uncertainty that arises from extrapolating data. In its revised analysis after consultation, the company used the Yu et al. (2014) data. However, the company was concerned that the 2014 data could be confounded because of crossover. The committee was aware that only 4 of the 113 patients had switched treatment and that the direction of any potential bias would be unknown. Given the small proportion of patients switching treatment it considered that any potential confounding was likely to be negligible. The committee recalled its preference for using the latest and most mature data from the dinutuximab alpha appraisal, noting that patient and clinical experts had agreed with this approach. It was aware that the 2014 analysis was not published but that the overall survival data had been considered by the European Medicines Agency in its regulatory assessment of dinutuximab alpha. It concluded that the 2014 data for isotretinoin were the most appropriate to use in the model.

Modelling clinical effectiveness of dinutuximab beta

Long-term benefit is the main source of uncertainty so a range of extrapolations are considered

3.12 The company extrapolated event-free and overall survival for the dinutuximab beta arm from 70 months to 10 years using a Gompertz parametric curve. The committee noted that the company assumed

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proportional hazards between dinutuximab beta and isotretinoin, which implied that the relative treatment effect is maintained over the lifetime of the model. The committee recalled that in the dinutuximab alpha appraisal the data were more mature and after 5 years the event-free and overall survival curves began to converge, with the initial separation of the time-to-event curves diminishing. Given that dinutuximab alpha and dinutuximab beta are derived from the same antibodies, it was possible that a similar effect may be seen in the dinutuximab beta trial after longer follow-up. The DSU explored other extrapolations that enabled modelling of more complex hazard functions, allowing for the relative treatment effect to vary over time. The committee recognised that the long-term benefit of dinutuximab beta was the main source of uncertainty in the appraisal. It therefore considered a range of plausible extrapolations.

Gompertz or spline models are the most plausible for overall survival, but all extrapolations are uncertain

3.13 The committee considered that the spline models fitted the overall survival data better at the early part of the curve than the parametric models. The clinical experts explained that most relapses occurred between 1 and 3 years, with relapses after 5 years being rare, and noted that none of the extrapolation curves for the dinutuximab beta arm fully captured this plateau from 5 years onwards. The committee recalled that in the 2014 analysis of ANBL0032, events did occur in the dinutuximab alpha arm after 5 years. But it was also aware that a plateau from about 7 years onwards was seen in the isotretinoin arm. The committee also noted that the point at which the plateau occurred in the extrapolated curves for the dinutuximab beta arm was at a lower survival rate than the Kaplan–Meier data showed. The DSU explained that this was because it was not possible for the models to fit to the exact shape of the curve, but the effect of different assumptions about long-term overall survival with dinutuximab beta was reflected in the scenario analyses exploring the effect of different cure thresholds. The scenario assuming a 5-year cure threshold for example would be equivalent to assuming that no further events occurred

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after 5 years, and therefore the plateau in this scenario would occur at a point closer to the actual Kaplan–Meier data. The committee noted that the DSU's Gompertz extrapolation showed a probability of survival at 10 years of 61%. It was the flattest survival curve, best reflecting the expected plateau, that is, that very few events would occur after 5 years. However, the committee considered that the spline model with 2 knots was also plausible, and this predicted a probability of survival at 10 years of about 59%. The company's Gompertz extrapolation showed a survival probability at 10 years that was between these 2 estimates. The committee concluded that the Gompertz or 2-knot spline extrapolations were the most plausible for overall survival, but all extrapolations were uncertain given the immaturity of the data.

Gompertz or spline models are the most plausible for event-free survival, but all extrapolations are uncertain

3.14 The committee considered that the spline models better fitted the event-free survival data at the early part of the curve than the parametric models. It preferred the DSU's extrapolation using the spline model with 1 knot. It also took into account the Gompertz extrapolation that the company considered best reflected the expected plateau after 5 years and had used in its original submission and in its updated analysis submitted in response to consultation. The clinical experts advised that the monthly risk of progression of less than 10% after 5 years predicted by the Gompertz extrapolation was clinically plausible because in their experience relapse after 5 years was not seen. The committee concluded that the 1-knot spline or the Gompertz extrapolation for event-free survival could be plausible, but all the extrapolations were uncertain.

Cure threshold

A 10-year cure threshold is preferred but others may be plausible

3.15 The committee was aware that the long-term benefits of immunotherapy were uncertain. It recalled that most relapses happened before 3 years and that relapses after 5 years were rare (see section 3.13). It also

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recalled that in the dinutuximab alpha appraisal data showed that relapses did occur between 5 and 10 years, mostly in the dinutuximab arm, but did not appear to occur beyond 10 years. Dinutuximab alpha was not recommended for routine NHS use and there was an appeal hearing in September 2016. The appeal panel recommended that a reasonable approach might be to consider a range of plausible cure points and explore the strengths and weaknesses of each of the points. The committee considered that the 10-year cure point in the company's model was appropriate because it reflected the fact that some events may occur between 5 and 10 years. However, the uncertainties in the extrapolations reflected the limitations of the clinical evidence driving the model. Therefore, other cure thresholds presented in the company's and DSU's scenario analyses could also be plausible. The committee considered that events may occur after 5 years because this was seen in the dinutuximab alpha data (see section 3.13), but it accepted that the exact relationship between dinutuximab alpha and beta was unknown. Therefore, the committee agreed that although its preferred assumption was a 10-year cure threshold, other cure points could be plausible. It concluded that it would consider a range of cure thresholds in its decision-making.

Costs

In the failure health state patients are likely to have chemotherapy for 1 year

3.16 The committee noted that patients have additional lines of chemotherapy after disease progression (see section 3.6) and the costs of this should be included in the model. In its additional analyses the company estimated the proportion of newly progressed patients having chemotherapy from the matched-adjusted individual patient data from APN311-302, which the DSU considered appropriate. The company assumed that these patients would have chemotherapy for 1 year. The clinical experts noted that some patients may have later lines of treatment, but agreed that assuming a 1-year treatment duration in the failure health state was reasonable. The

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committee therefore concluded that this assumption in the company's model was appropriate.

Infection-related costs are appropriately included in the model

3.17 The committee, recalling the rate of infection in APN311-302 (see section 3.7), asked that the cost of infection-related hospitalisation, including any infection-related complications, should be included in the model, in addition to the cost of an inpatient stay for infusion. These costs were included in the additional analyses. The costs of the increased infections associated with taking interleukin-2 were reflected in the company's scenario analyses including concomitant interleukin-2. The committee concluded that the costs of treating infections arising from treatment were appropriately included in the model.

The changes to the company's cost assumptions are reasonable

3.18 The company adjusted the cost assumptions in its base case in line with the committee's request.

- It estimated the cost for dinutuximab beta based on a weighted average that took into account the proportion of patients in different body surface area categories in APN311-302, rather than the number of vials needed for an average body surface area.
- It adjusted the costs of chemotherapy to include wastage.
- It calculated the administration costs per cycle using the cost of an inpatient stay rather than a chemotherapy procurement cost.
- It revised the associated resource use for patients who have had chemotherapy but are still alive and in the failure health state.

The DSU commented that the changes to the cost assumptions in the company's original model had been implemented correctly. The committee concluded that the company's revised cost assumptions were reasonable. It noted however, that the ICERs presented did not appropriately account for end of life costs, which would reduce the ICERs by approximately £1000.

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It is appropriate to include a discontinuation rate; the DSU's approach is preferred

3.19 In its additional evidence submitted during consultation, the company applied a treatment discontinuation rate to the model to account for people reducing their dose or stopping treatment permanently in clinical practice. The company used the number of patients who had stopped treatment because of toxicity or tolerability in APN311-302. The DSU noted that the company's approach may have double-counted patients who stopped treatment because of toxicity and whose disease then progressed, who would already be captured by event-free survival data. This would therefore underestimate the proportion of patients having the treatment in each cycle. The DSU instead used the actual number of patients having treatment in each cycle from APN311-302 (patients not having interleukin-2) to model treatment discontinuation. The committee considered it was reasonable to take into account discontinuation because of toxicity or tolerability and concluded that the DSU's method was more appropriate because it avoided double-counting.

Utilities

The Ara et al. algorithm is appropriate to estimate age-specific UK EQ-5D values in the model

3.20 The committee noted that health-related quality of life was not captured in APN311-302. The company had originally reduced the UK EQ-5D general population values to reflect the fact that patients in the model have neuroblastoma. The committee recalled that the dinutuximab alpha appraisal included a published algorithm by Ara et al. (2010), which was used to estimate mean EQ-5D health state utility values for the general population. The ERG considered this method to be more appropriate than using a logistic regression. On request, the company used Ara et al. to estimate utility values in its additional analyses. The committee concluded that the Ara et al. algorithm was appropriate to estimate age-specific UK EQ-5D values in the modelling, which the company had done.

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Discount rate

The 1.5% discount rate used in the company's base case is appropriate

3.21 The committee recalled that in the dinutuximab alpha appraisal it concluded that 'the non-reference case discount rate could apply because the dinutuximab alpha regimen could be considered to cure neuroblastoma in a small proportion of patients'. It also concluded that 'this discount rate should be applied to both costs and outcomes in line with the current methods guide'. The committee considered that the same reasoning applied for dinutuximab beta and it concluded that the 1.5% discount rate modelled by the company was appropriate.

Results of the cost-effectiveness analyses

The ICERs presented are above the range usually considered cost effective

3.22 The committee considered the incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) gained using its preferred assumptions:

- the 2014 trial data for isotretinoin (see section 3.11)
- Gompertz or 2-knot spline overall survival extrapolation (see section 3.13)
- Gompertz or 1-knot spline event-free survival extrapolation (see section 3.14)
- including a range of cure thresholds (see section 3.15)
- excluding concomitant interleukin-2 (see section 3.6)
- the DSU's approach to modelling treatment discontinuation (see section 3.19)
- the most appropriate cost and utility inputs (see sections 3.16 to 3.18 and 3.20).

The ICERs for dinutuximab beta compared with isotretinoin using the committee's preferred assumptions and the confidential commercial arrangement for dinutuximab beta were above £40,000 per QALY gained

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(the exact figures for the different extrapolation curves and cure thresholds are commercial in confidence and cannot be reported). This estimate was subject to other factors considered relevant by the committee (as summarised in section 3.28).

Long-term survival benefit with dinutuximab beta is uncertain and is the main driver of the cost-effectiveness analysis

3.23 The committee noted that different extrapolations of long-term survival had a large effect on the ICER, even though the actual difference in the survival rate predicted by the extrapolations was small. The company expressed concern about the sensitivity of the ICERs to small differences in curve estimates. The committee was aware that the long-term survival estimate was the main source of uncertainty in the appraisal and it had therefore considered a range of plausible extrapolations (see section 3.12) and cure thresholds (see section 3.15). It also recognised the effect of small changes in survival estimates given the small numbers of patients in the analysis, and that because of this, long-term benefit was the main driver of the cost-effectiveness analysis.

End of life

Dinutuximab beta does not meet the end-of-life criteria

3.24 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's Cancer Drugs Fund technology appraisal process and methods. The committee noted that the modelled life expectancy for patients having isotretinoin alone was about 31 to 34 years, which did not meet the criterion for short life expectancy. The modelled incremental gain, using the DSU's range of most plausible ICERs and the latest data available for isotretinoin, was between 3 and 5 years, which met the criterion for survival gain. The committee acknowledged that the extent of survival gain potentially offered by dinutuximab beta was substantial. But it recognised that this estimate was uncertain and it could not be confident of the extent of proportional gain in

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relation to the high life expectancy. The committee therefore concluded that the end-of-life criteria were not met.

Cancer Drugs Fund

Data collection in the Cancer Drugs Fund would not resolve uncertainty about dinutuximab beta's long-term benefit

3.25 The committee had previously concluded that given dinutuximab beta's promising clinical benefit in the trial and the potential for longer-term data to be available in 2 to 3 years, it would consider dinutuximab beta for the Cancer Drugs Fund. After consultation the company reported that an amendment to the APN311-302 trial protocol would be needed to collect further follow-up data, and this amendment could take up to 2 years. The prospective data collection offered by the safety registry, set up as required by the European Medicines Agency, would also not produce timely long-term data. Establishing a UK registry was also considered. But given the small number of UK patients the committee considered that any data generated would not resolve uncertainty, given the disproportionate effect of small patient numbers on overall survival estimates (see section 3.23). The committee agreed that the feasibility of collecting the data needed to address the uncertainties was limited. The committee therefore concluded that the Cancer Drugs Fund would not be the appropriate way to address the clinical uncertainties.

Other factors

Some health-related benefits are not captured in the economic model

3.26 The committee considered whether there were any health-related benefits that were not captured in the economic analysis. It was aware that neuroblastoma is a devastating disease that affects children and young adults as well as their families and carers. The committee acknowledged that there were uncaptured health-related benefits. These included reduced quality of life because of the effect of stress and depression caused by the disease on young patients and their families, as well as the

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devastating effects of bereavement on families. It discussed the need to balance the importance of improving the lives of children and their families with fairness to people of all ages, and noted NICE's social value judgements: principles for the development of NICE guidance, which emphasise the importance of considering the distribution of health resources fairly within society as a whole, as well as considering factors other than relative costs and benefits alone.The committee noted the fact that patients were children was partly addressed by accepting a 1.5% discount rate for costs and QALYs (see section 3.21). Despite this, it recognised the severity of the disease and the importance of generating potentially life-long health benefits for this patient population. The committee was not presented with any quantitative data to show distinct and substantial uncaptured health-related benefits. However, it was confident that there were health-related benefits that were not captured in the company's model, which needed to be accounted for in its decision-making.

The committee is prepared to be flexible in its decision-making given the rarity and severity of the disease

3.27 Although dinutuximab beta is an orphan drug because of the small number of patients affected by neuroblastoma, it could not be considered through the highly specialised technologies programme because it is not commissioned through a highly specialised service. The committee acknowledged the difficulty of appraising orphan drugs for rare conditions, which is not helped by the limited potential for generating robust long-term data and the disproportionate effect of small numbers of patients on the cost-effectiveness analyses (see sections 3.25 and 3.23). When developing the social value judgements, the Citizens Council considered that rarity alone is not a mitigating factor for accepting high ICERs, but the committee should consider taking into account other factors such as disease severity in its decision-making. The committee concluded the severity of high-risk neuroblastoma should be considered in its decision-making.

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Dinutuximab beta is a cost-effective use of NHS resources

3.28 The committee was aware of the uncertainty around the long-term clinical benefit of dinutuximab beta and the lack of practical or timely solutions to resolve this (see section 3.25), but it acknowledged that the potential survival gain offered by dinutuximab beta was substantial. It recognised that the marketing authorisation for dinutuximab beta was granted under exceptional circumstances because the data were immature. Also, because clinical benefit with dinutuximab alpha has been shown, immunotherapy (dinutuximab alpha or beta) has become standard care in some countries and it was therefore considered unethical not to offer immunotherapy within a trial to patients with neuroblastoma. It also acknowledged the company's efforts in exploring the potential data collection options and in adapting its commercial arrangement. In addition to the ICERs presented, the committee considered:

- the patient population (see section 3.26)
- the number of patients affected (see section 3.27)
- the severity of the disease and the painful and debilitating current treatments (see section 3.1)
- the potential for a significant survival benefit with dinutuximab beta (see section 3.24)
- the end of life costs not captured in the ICERs (see section 3.18) and
- the uncaptured benefits in the analysis (see section 3.26).

The committee concluded that taking into account all these factors, it was able to recommend dinutuximab beta as a cost-effective use of NHS resources.

3.29 No equality issues were identified.

4 Implementation

Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information

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Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.1 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has high-risk neuroblastoma and the doctor responsible for their care thinks that dinutuximab beta is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh
Chair, appraisal committee
July 2018

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6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Orsolya Balogh, Anna Brett
Technical Leads

Fay McCracken, Nwamaka Umeweni
Technical Advisers

Kate Moore
Project Manager

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