NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Dinutuximab beta for treating neuroblastoma

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using dinutuximab beta in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using dinutuximab beta in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 29 May 2018

Second appraisal committee meeting: 12 June 2018

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Dinutuximab beta is not recommended within its marketing authorisation for people aged 12 months and over, that is, for treating high-risk neuroblastoma after at least a partial response from induction chemotherapy, followed by myeloablative therapy and autologous stem cell transplant, and for treating relapsed or refractory neuroblastoma, with or without residual disease.

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 new option for maintenance treatment of the disease.

An indirect comparison with isotretinoin suggests that dinutuximab beta increases overall survival and the length of time before the disease progresses, compared with current treatment. But there is substantial uncertainty about its long-term benefits, which has a large impact on the cost-effectiveness estimates.

Dinutuximab beta does not meet NICE's criteria for a life-extending treatment at the end-of-life. However, the importance of the potential benefit in this population of children was acknowledged. The cost-effectiveness estimates take the uncertainty about long-term benefit into account, and assume that relapse after 5 years is rare. But the most

plausible estimate (£62,300 to £79,900 per QALY gained) is considered to be much higher than what NICE normally considers a cost-effective use of NHS resources. So dinutuximab beta cannot be recommended for routine use in the NHS for high-risk neuroblastoma.

Considering the promising clinical benefit with dinutuximab beta, a period of time in the Cancer Drugs Fund would provide the best opportunity for data collection to address clinical uncertainties. However, dinutuximab beta does not currently have the potential to be cost effective, so cannot be recommended for use within the Cancer Drugs Fund.

Dinutuximab beta also has a marketing authorisation to treat relapsed or refractory disease. However, this population is not relevant to current NHS practice, and therefore evidence was not considered in this population.

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).' There were 'exceptional circumstances' concerning the approval of this medicine. This happens when the applicant can show that they are unable to provide comprehensive data on the efficacy and safety of the medicine for which authorisation is being sought, due to 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 • 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 prior to the first infusion of dinutuximab beta and the second 5-day course should start concurrently with 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 by the patient, 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. Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The appraisal committee (section 5) 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.

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 impact on children and young people and their families and carers. They also explained that children and young people with the condition have anxiety about their illness and treatment as well as discomfort and pain from the disease. The committee noted that treatment can involve many hospital visits and stays causing disruption to school, work and family life. The patient experts explained that 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 committee 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 clinical and patient experts explained that a child's death has a significant effect on family members. 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

Maintenance therapy for high-risk neuroblastoma is dinutuximab beta plus isotretinoin in a clinical trial, but isotretinoin is the relevant comparator for decision-making

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, who have had at least a partial response from

induction chemotherapy followed by myeloablative therapy and autologous stem cell transplant, were enrolled in the immunotherapy phase of the 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 clinical practice because it is used only in research as part of a clinical trial and is not routinely commissioned. The committee understood that before dinutuximab beta was available through 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 after at least a partial response from induction chemotherapy, followed by myeloablative therapy and autologous stem cell transplant.

Patients with relapsed or refractory neuroblastoma have already had dinutuximab beta in clinical practice

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 almost all patients with relapsed or refractory neuroblastoma have had first-line dinutuximab beta in the clinical trial (see section 3.2). The committee concluded that almost all patients having treatment for relapsed or refractory neuroblastoma in clinical practice have had dinutuximab beta as a prior treatment in the clinical trial (APN311-302).)

Clinical trial evidence

APN311-302 is the best available evidence for dinutuximab beta in high-risk neuroblastoma, but is not in line with the scope

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 is 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 considered that the trial results showed that concomitant interleukin-2 did not improve event-free or overall survival, and that despite its limitations, APN311-302 represented the best available evidence for dinutuximab beta. But it concluded that because all patients in the trial had dinutuximab beta, the evidence did not inform the decision problem as set out in the NICE scope.

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

3.5 The evidence for the population with relapsed or refractory disease came from 2 observational studies of dinutuximab beta with isotretinoin and interleukin-2: APN311-202 and APN311-303. The committee acknowledged that in APN311-202, 36.8% of people with relapsed disease had not had an event at 3 years compared with 44.6% of people with refractory disease. In APN311-303, 24.1% of people with relapsed disease had not had an event compared with 29.1% of people with refractory disease. Overall survival was similar for people enrolled in APN311-202 and in APN311-303 at the reported time points. The ERG stated that given the small numbers of patients in each subgroup, the observational nature of both studies, and the high degree of censoring in each study, the event-free and overall survival results should be interpreted with caution. The clinical experts explained that people in the NHS who have relapsed disease are likely to have had dinutuximab beta as part of their multi-agent, multimodal first-line therapy (see section 3.3). The committee noted that none of the patients in APN311-302 and APN311-303 had previous dinutuximab beta, and comments from clinical experts that patients whose disease has relapsed after dinutuximab beta have not been eligible for further dinutuximab beta within any clinical trial. The company explained that it does not support retreatment with dinutuximab beta in the relapsed or refractory population, and that there are no studies planned for patients with relapsed or refractory disease who have had initial treatment with dinutuximab beta. The committee agreed that the populations in APN311-202 and APN311-303 do not represent the population with relapsed or refractory disease who would have dinutuximab beta in NHS clinical practice. Therefore it concluded, with agreement from the company and the experts, that the 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, which 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 less toxicity 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 The committee noted that 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 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

The company and DSU's matched-adjusted indirect comparison results show that dinutuximab beta improves event-free and overall survival compared with isotretinoin

3.8 There was no direct evidence comparing dinutuximab beta with isotretinoin. In response to the committee's request, the company provided a matched-adjusted indirect comparison using data from the ANBL0032 trial of dinutuximab alpha compared with isotretinoin, as reported by Yu et al. (2010). For the dinutuximab beta arm of the analysis, the company pooled data from both arms of APN311-302 because patients in both arms of the trial 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, and the results showed that dinutuximab beta improved overall and event-free survival compared with isotretinoin. The analysis produced a hazard ratio for event-free survival of 0.68 at 70 months (5.8 years; the latest point at which trial data were available) for dinutuximab beta compared with isotretinoin, with a 95% confidence interval (CI) of 0.62 to 0.8. Overall survival at 70 months showed a hazard ratio of 0.63 (95% CI 0.54 to 0.86) for dinutuximab beta compared with isotretinoin. However, the DSU explained that the hazard ratios had been generated assuming the data follows an exponential distribution, which it considered unlikely because the estimates of the hazard ratios would vary according to how the interval is chosen. It also noted that it was not possible to adjust the analysis to account for previous consolidation therapy, which differed between the 2 trials and was a potential prognostic factor, and that this therefore may bias the results (although the direction or size of the potential bias was not known). The DSU 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. The results were similar to the company's. The committee concluded that the DSU's matched-adjusted Kaplan–Meier survival curves showed that dinutuximab beta improved event-free and overall survival compared with isotretinoin.

The company's economic model

The structure of the model is appropriate

3.9 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.

Modelling clinical effectiveness of isotretinoin

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

3.10 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 reduces the uncertainty that arises from extrapolating data. The committee noted that the company had produced a scenario analysis on request, using the 2014 data, but that it had continued to extrapolate the isotretinoin arm beyond 70 months rather than use the actual trial data. The company was concerned that the 2014

data could be confounded because of crossover. The committee was aware that only 4 out of the 113 patients had switched treatment and that these patients had been censored in the analysis. It recognised that the direction of any potential bias would be unknown, and given the small proportion of patients switching treatment it considered any potential confounding would likely 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 had been considered by the European Medicines Agency in its regulatory assessment of dinutuximab alpha. It concluded that the 2014 data for isotretinoin was the most appropriate to use in the model.

The DSU's method of using trial data in the model is more appropriate than the company's extrapolation

3.11 The committee considered the differences between the Kaplan–Meier and extrapolated curves for isotretinoin. It noted that the company's extrapolation of event-free and overall survival in the isotretinoin arm using Gompertz parametric curves showed a levelling-out, or plateau, of events at 3–4 years and then an increase in events at 6 years for event-free survival and at 7 years for overall survival. The clinical experts explained that most relapses occurred between 1 and 3 years; relapses after 5 years were rare, and an increase in relapses after 5 years as modelled by the company was not clinically plausible. Also, actual data from the 2014 analysis of ANBL0032 showed that there were no events after approximately 7 years for people having isotretinoin. The DSU had used this data in the economic model, which meant that no extrapolation was needed for the isotretinoin arm. The committee concluded that the company's extrapolation of event-free and overall survival data for the isotretinoin arm of the analysis was not clinically plausible, and the DSU's method of using actual trial data was more appropriate.

Modelling clinical effectiveness of dinutuximab beta

Long-term benefit is the main source of uncertainty and a key driver of the cost-effectiveness analysis, 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 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. It noted that 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 and was a key driver of the cost-effectiveness analysis. Therefore it considered a range of plausible extrapolations.

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

3.13 The committee considered that the spline models fitted the event-free and overall survival curves better at the early part of the curve than the parametric models. The clinical experts noted that none of the extrapolation curves for the dinutuximab beta arm fully captured the plateau expected from 5 years onwards. The committee recalled that in the 2014 analysis of ANBL0032 events occurred in the dinutuximab alpha arm after 5 years. However, it was also aware that a plateau from about 7 years onwards was seen in the Kaplan–Meier curves from the trial data for isotretinoin. The committee also noted that the point at which the

plateau occurred in 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 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 had shown a survival probability at 10 years that was between these 2 estimates. For event-free survival, the committee considered that the spline models better fitted the data, and it therefore preferred the DSU's extrapolation using the spline model with 1 knot to the company's Gompertz extrapolation. The committee concluded that the Gompertz or 2-knot spline extrapolations were the most plausible for overall survival and it preferred the 1-knot spline extrapolation for event-free survival, but all of the extrapolations were uncertain given the immaturity of the trial data.

Cure threshold

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

3.14 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 3.11). It also recalled that in the dinutuximab alpha appraisal relapses did occur between 5 and 10 years, mostly in the dinutuximab arm, but did not

appear to continue beyond 10 years. Dinutuximab alpha was not recommended for routine NHS use and there was an appeal hearing in September 2016. The committee recalled that 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. In the company's scenario analyses, the incremental cost-effectiveness ratios (ICERs) increased as the cure threshold lowered. This was in contrast to the DSU's scenario analyses and the dinutuximab alpha appraisal, in which lowering the cure threshold also lowered the ICER. The DSU explained that the opposite effect was seen in the company's analysis because of the way the isotretinoin arm had been modelled, which the committee had agreed was not appropriate (see section 3.11). The committee considered that events may occur after 5 years because this was seen in the dinutuximab alpha data (see sections 3.11 and 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 thresholds in its decision-making.

Costs

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

3.15 The committee noted that patients have additional lines of chemotherapy after disease progression (see section 3.6) and that 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 committee therefore concluded that this assumption in the company's model was appropriate.

Infection-related costs are appropriately included in the model

3.16 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 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

3.17 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 committee noted the DSU's comment that the changes to the cost assumptions in the company's original model had been implemented correctly. It concluded that the company's revised cost assumptions were reasonable.

Utilities

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

3.18 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.

Discount rate

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

3.19 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 most plausible ICER is above the range considered cost effective

3.20 The company's base-case probabilistic ICER for dinutuximab beta with isotretinoin compared with isotretinoin alone was £24,684 per quality-adjusted life year (QALY) gained. This was based on a 10-year cure threshold, no concomitant interleukin-2 in line with clinical opinion, and the committee's preferred costs and utilities assumptions (see sections 3.14 to 3.19), but also a survival extrapolation in the isotretinoin arm from the 2010 data which the committee had concluded was implausible (see section 3.11). The committee noted that using the 2014 data for isotretinoin in the model, as the DSU had done, increased the probabilistic ICER to £78,162 per QALY gained. It was aware that the 2014 analysis was not adjusted for the crossover of 4 patients, but it considered that any potential confounding was negligible (see section 3.10) and it could not be known if there would be an impact on the ICER or in what direction. Incorporating the event-free and overall survival extrapolation for dinutuximab beta that the committee considered most plausible (see section 3.13) produced an ICER of £79,493 per QALY gained using Gompertz for overall survival, and £79,935 per QALY gained using the 2-knot spline. The committee recognised that other cure thresholds could be plausible (see section 3.14), and was aware that this could reduce the ICER to £62,309 per QALY gained. The committee concluded that the most plausible ICER is likely to lie between £62,300 and £79,900 per QALY gained, and that this was higher than what NICE normally considers to be a cost-effective use of NHS resources (that is, between £20,000 and £30,000 per QALY gained).

Long-term survival benefit with dinutuximab beta is uncertain; the committee's preferred assumptions are optimistic

3.21 The committee noted that other extrapolations 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 DSU considered it was important to reflect the uncertainty in the data in its probabilistic sensitivity analysis. The committee noted that the marketing authorisation for dinutuximab beta was granted under exceptional circumstances because the data were immature. It was aware of the effect of small changes in survival estimates given the small numbers of patients in the analysis. The committee was also aware that the long-term survival estimate was the key 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 3.14). However, it was also aware that all other extrapolations increased the ICER still further. So it considered that its preferred assumptions were optimistic about the long-term benefit with dinutuximab beta.

End of life

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

3.22 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 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 30 and 53 months, 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 relation to the high life expectancy. The committee therefore concluded that the end-of-life criteria were not met and dinutuximab beta could not be recommended for routine use.

Cancer Drugs Fund

Dinutuximab beta does not currently meet the criteria for inclusion in the Cancer Drugs Fund; a proposal from the company is welcomed

3.23 Having concluded that dinutuximab beta could not be recommended for routine use, the committee then considered if it could be recommended for treating high-risk neuroblastoma within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting the addendum to the NICE process and methods guides. The committee understood that the company had not made a case for dinutuximab beta to be considered for the Cancer Drugs Fund, but that it was willing to consider this potential route. The committee understood that dinutuximab beta had been available in England since 2010 and that the registry (SAFARY) established as required by the exceptional marketing authorisation required the company to produce annual results for the European Medicines Agency. It also noted that there would be a cohort of patients from APN311-302 with 7 years' follow-up in 2 to 3 years' time, and that together with the registry data this could help to resolve some of the uncertainty about the long-term benefit of dinutuximab beta. However, given that the range of most plausible ICERs was between £62,300 and £79,900 per QALY gained (see section 3.20), which was substantially higher than the range normally considered a cost-effective use of NHS resources, the committee did not consider that there was proven plausible potential to satisfy the criteria for routine use. Nevertheless, given the promising clinical benefit shown by dinutuximab beta so far in the trial data and the potential for longer-term data within a 2–3 year period, the committee would welcome a proposal from the company for including dinutuximab beta in the Cancer Drugs Fund. The committee considered a period of time in the Cancer Drugs Fund would be the best opportunity for data collection to address the clinical uncertainties, including collecting data on biomarkers that could potentially identify subgroups more likely to benefit from treatment. But because it had not seen plausible potential for

cost-effectiveness, the committee could not currently recommend dinutuximab beta for use within the Cancer Drugs Fund as an option for people with high-risk neuroblastoma.

Other factors

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

3.24 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 devastating effects of bereavement on families. It noted the severity of the disease and the importance of generating health benefits for this patient population. The committee was not presented with any data to show distinct and substantial uncaptured health-related benefits. It was confident that there were health-related benefits that were not captured in the company's model, but it was difficult to establish how the cost-effectiveness estimates might be affected. Even taking these uncaptured health benefits into account, given the most plausible cost-effectiveness estimates, this would not change the committee's decision.

Long-term clinical benefit is too uncertain and the cost-effectiveness estimates too high to justify deviating considerably from NICE principles

3.25 The committee was fully aware of the patient population in this appraisal being young children and therefore carefully considered this aspect in its deliberations. 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 3.19). Despite this, given 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 3.22), and the potential uncaptured benefits, the committee

wished to be as flexible as it could in the ICER it was prepared to accept. However, it was aware of the significant uncertainty around the long-term clinical benefit of dinutuximab beta and that this was a key driver of the cost-effectiveness estimate (see section 3.21). The committee concluded that the ICERs were currently too high to justify deviating considerably from what NICE normally considered a cost-effective use of NHS resources.

3.26 No equality issues were identified.

Conclusion

Dinutuximab beta cannot be recommended

3.27 The committee acknowledged that dinutuximab beta would be a good candidate for the Cancer Drugs Fund. However it could not recommend dinutuximab beta as a cost-effective use of NHS resources for treating high-risk neuroblastoma because the range of most plausible ICERs was substantially higher than £30,000 per QALY gained, and the end-of-life criteria were not met.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. 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
April 2018

5 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.

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