NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Dinutuximab for treating high-risk neuroblastoma

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using dinutuximab 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, and 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 draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 8) and the public. This document should be read along with the evidence base (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 provisional 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 determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using dinutuximab in the NHS in England.

For further details, see the Guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 25 November 2015

Second Appraisal Committee meeting: 27 January 2016

Details of membership of the Appraisal Committee are given in section 7, and a list of the sources of evidence used in the preparation of this document is given in section 8.

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

1 Appraisal Committee's preliminary recommendations

1.1 Dinutuximab, in combination with granulocyte-macrophage colony-stimulating factor, interleukin-2 and isotretinoin, is not recommended within its marketing authorisation, for treating high-risk neuroblastoma in children and young people between 12 months and 17 years whose disease has at least partially responded to induction chemotherapy, followed by myeloablative therapy and autologous stem cell transplant.

1.2 Children and young people whose treatment with dinutuximab was started within the NHS before this guidance was published should be able to continue treatment until they and their NHS clinician consider it appropriate to stop. This decision should be made jointly by the clinician and the child or young person or their parents or carers.

2 The technology

2.1 Dinutuximab (Unituxin, United Therapeutics) is a human–mouse monoclonal antibody produced in a myeloma cell line (SP2/0) using recombinant DNA technology. It has a marketing authorisation for treating 'high-risk neuroblastoma in patients aged 12 months to 17 years who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and autologous stem cell transplantation'. Dinutuximab is given as part of a 6-course regimen which includes granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 and

isotretinoin. It is administered at a daily dose of 17.5 mg/m^2 on days 4–7 during courses 1, 3 and 5 (each course lasting approximately 24 days) and on days 8–11 during courses 2 and 4 (each course lasting approximately 28 days). Course 6 includes treatment with isotretinoin alone.

2.2 The most frequently occurring adverse reactions reported in the summary of product characteristics were low blood pressure (67%), pain (66%), hypersensitivity (56%), fever (53%), itching (49%), capillary leak syndrome (45%), anaemia (34%), low blood potassium (41%), decreased platelet count (40%), low blood sodium (37%), increased alanine aminotransferase (35%), decreased lymphocyte count (34%) and decreased neutrophil count (31%). For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The list price in the company's submission for a single infusion of dinutuximab (17.5 mg) costs £6390 (excluding VAT). The cost of a complete course of dinutuximab treatment is £127,800, excluding the cost of treatments it is given with. The company estimated that the total cost when isotretinoin, GM-CSF [using the US list price converted to pounds sterling] and interleukin-2 are included is £135,404. Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

The Appraisal Committee (section 7) considered evidence submitted by United Therapeutics and a review of this submission by the Evidence Review Group (ERG; section 8).

Clinical effectiveness

3.1 The company's submission included 1 international, multicentre, partly randomised, event-driven study (ANBL0032; n=226). This

study evaluated the clinical efficacy of dinutuximab plus interleukin-2, granulocyte-macrophage colony-stimulating factor (GM-CSF) and isotretinoin compared with isotretinoin alone (the standard therapy) in patients with high-risk neuroblastoma. The trial inclusion criteria defined high-risk neuroblastoma according to the Children's Oncology Group definitions. The trial included patients with high-risk neuroblastoma who were 31 years or younger (although no patient older than 15 years was recruited), who had completed induction therapy with at least a partial response to treatment, before autologous stem cell transplant and radiotherapy. Other inclusion criteria were that patients did not have progressive disease, had a life expectancy of 2 months or more and adequate renal, liver, cardiac, pulmonary and central nervous system function. Patients were randomised to the dinutuximab regimen (n=113) or isotretinoin (n=113). In the same study, 25 additional patients who had biopsy-proven disease were not randomised. Instead, they were assigned to have the dinutuximab regimen, but their results were excluded from the primary efficacy analysis.

3.2 The trial was originally estimated by the US National Institutes for Health and Children's Oncology Group to run for 4 years. Randomisation could be stopped early based on a safety monitoring committee's decision that the dinutuximab regimen met pre-defined criteria for superiority over standard therapy as measured by event-free survival, the primary outcome of the trial. The criteria were a relative risk of event-free survival of 1.6 at 3 years between isotretinoin and the dinutuximab regimen. The company planned to evaluate overall survival as a secondary outcome using a gatekeeping approach, whereby it would calculate overall survival without first detecting a statistically significant difference in event free survival. The trial randomisation was stopped early in January 2009. According to the company, the trial

should not have been stopped because the stopping criteria had not been reached. The June 2009 analysis results suggested that patients having the dinutuximab regimen had greater event-free survival at 2 years (66.3% compared with 46.4%, p=0.01) and greater overall survival (86.2% compared with 74.5%, p=0.02) than those having isotretinoin.

3.3 After the 2009 analysis, randomisation was stopped and patients continued to be monitored. Of the 226 patients randomised in the trial, only 4 patients crossed over to have dinutuximab after having isotretinoin. The results from those patients were censored. In March 2014 the European Medicines Agency asked for an updated analysis for 225 of the original 226 patients in the pivotal clinical trial. Event-free survival and overall survival were analysed 4 years after the end of randomisation using longer-term follow-up data. The 2014 results suggested that patients having the dinutuximab regimen had a smaller event-free survival advantage (59.3 compared with 48.3%, p=0.15) and a smaller overall survival advantage (75.1% compared with 61.0%, p=0.03) at 4 years than those having isotretinoin. The company stated in its submission that the analysis at 4 years was inadequately powered to detect statistical differences between immunotherapy and standard therapy, as randomisation was stopped early.

3.4 The company also presented a post-hoc subgroup analysis based on Curie score, which predicts the extent and severity of disease based on a full body scan using radioactive isotopes. A score greater than 0 indicates a neuroblastoma tumour and a score of 0 indicates that no tumour was detected on the scan. The Curie scores of 197 patients enrolled in ANBL0032 were known: 167 patients had a Curie score of 0 and 30 patients had a score greater than 0. The company evaluated the outcomes after treatment with the dinutuximab regimen (n=100) compared with

isotretinoin (n=97). Event-free survival was greater in both treatment arms in patients with a Curie score of 0 than in patients with a Curie score greater than 0. Event-free survival at 3 years for patients having the dinutuximab regimen was greater in patients with a Curie score of 0 than in patients with a Curie score greater than 0 (70.5% compared with 26.7%; $p<0.001$). For patients having isotretinoin, event-free survival was similar in both Curie score groups (47.5% compared with 40.0%; $p=0.22$). The dinutuximab regimen appeared to be more effective than isotretinoin in people with a Curie score of 0, but the treatment benefit was not maintained in patients with a Curie score greater than 0. The company noted that the number of patients with a Curie score greater than 0 was small (n=30) and therefore the results should be interpreted with caution.

3.5 The most common adverse reactions reported in the dinutuximab arm of ANBL0032 were neuropathic pain (52%), infection (39%), fever without neutropenia (39%), low potassium blood concentration (35%), hypersensitivity reaction (25%), low sodium blood concentration (23%), abnormal alanine aminotransferase (23%), acute capillary leak syndrome (23%), and hypotension (18%). The most common adverse reaction with isotretinoin was infection (22%). According to the company, most adverse reactions were self-limiting and resolved after stopping treatment. The ERG commented that the adverse reactions reported in the trial were serious, but were generally acute and resolved quickly unless death occurred.

3.6 The trial did not collect health-related quality of life data.

Cost effectiveness

3.7 The company's submission included a partitioned survival model that compared the dinutuximab regimen with isotretinoin alone. The model had 3 health states:

- the 'stable' health state, in which patients were alive with no disease relapse, progression or secondary cancer
- the 'failure' health state, in which patients were alive but with disease relapse, progression or secondary cancer
- death.

Unlike a Markov model, which models transitions between health states explicitly using transition probabilities, a partitioned survival model calculates the proportion of patients in each treatment arm at any time after starting treatment, using parametric survival curves fitted to empirical data on overall survival and progression free survival over time.

3.8 All patients entered the model in the stable state at age 4 years and 60% of the patients were male. The company used quality-adjusted life years (QALYs) to capture health effects from an NHS and personal social services perspective. It discounted benefits and costs by 3.5% in its base-case analysis, and used a lower discount rate of 1.5% for health outcomes only in a scenario analysis. All patients were assumed to die by 100 years.

3.9 The company used the results of the ANBL0032 analyses from 2009 to inform its base case. The 2-year event-free survival (66% for the dinutuximab regimen; 46% for isotretinoin) and overall survival rates (86% for the dinutuximab regimen; 75% for isotretinoin) were used. The company justified using the 2-year time point because it represented the period before randomisation was broken when the trial stopped early and therefore was less

prone to bias. The company fitted parametric survival curves to the Kaplan–Meier event-free and overall survival data from ANBL0032 for the first 5 years of the model. These were used to identify the number of patients in each health state at monthly intervals with a half-cycle correction. In its base case, the company fitted a Gompertz survival model to the event-free survival Kaplan–Meier curve and an exponential function to the overall survival Kaplan–Meier curve.

3.10 The company assumed that after 5 years, patients who remained event-free were cured. The company did not apply a parametric model after 5 years. Instead, the company assumed that mortality, quality of life, and relapse rates reverted to those of the general population, taking into account potential morbidity affecting quality of life and resource use among patients surviving neuroblastoma. For patients who were in the failure health state after year 5, the company applied a monthly mortality probability of 5.1% in the model. In the failure health state, patients had topotecan combination treatment every month until death.

3.11 As health-related quality of life data were not collected in ANBL0032, the company searched for relevant studies that included health-related quality of life data for patients with neuroblastoma. The company did not find any studies reporting health state-specific utilities in patients with neuroblastoma, but it found a study that measured the health-related quality of life of patients who had tumours of the brain and central nervous system. Utility values from Barr et al. (1999) were assigned to the stable (0.81) and failure (0.56) health states in the model for the first 5 years. After 5 years, patients in the failure state continued to have a health utility of 0.56, whereas patients in the stable state were assumed to have similar characteristics to those of the general population (based on Ara et al. 2000) but with a 13% reduction in

utility (based on Portwine et al. 2014) to account for potential morbidity in patients surviving neuroblastoma. It chose the Portwine study because it included patients with neuroblastoma and had the largest number of patients (n=99) of the studies identified as potential sources for utility data.

3.12 The company applied no administration cost in the model for isotretinoin, because it is self-administered. The administration cost per cycle of GM-CSF was estimated to be £142.50, which was based on an assumption that 75% was self-administered and 25% was administered by a nurse (nurse costs from the Personal and Social Services Research Unit 2014). For dinutuximab and interleukin-2, administration costs were based on the NHS reference costs for procuring inpatient chemotherapy drugs for regimens in band 10 (code SB10Z; £1908). The company used the same cost for topotecan, which patients had after disease progression in the model. The drug costs used in the model were based on the number of vials needed for an average body surface area of 0.65 metre^2.

3.13 The deterministic incremental cost-effectiveness ratio (ICER) estimated by the company's model for the dinutuximab regimen compared with isotretinoin alone was £37,423 per QALY gained. The probabilistic ICER was £38,128 per QALY gained. The company's probabilistic analysis showed that at a maximum acceptable amount for an additional QALY of £30,000, the dinutuximab regimen had a 27% chance of being cost effective compared with isotretinoin alone.

3.14 The company did a series of deterministic one-way sensitivity analyses to assess the effect of varying the discount rate, costs, utility estimates and clinical data in the model. The ICER was most sensitive to changes in the discount rate (£13,153 and £60,747 per

QALY gained using a 0% and 6% discount rate, respectively). Changing the price of dinutuximab also affected the ICER (£31,309 and £44,173 per QALY gained using a price of £5176 and £7730, respectively).

3.15 The company performed a series of scenario analyses. The key drivers of the cost-effectiveness results were the estimates of event-free and overall survival used in the model (that is, whether they were derived from the 2009 or 2014 data analysis of ANBL0032). When the 2014 data and parametric survival curves applied up to year 5, this resulted in 2.85 incremental life years gained (that is, 34.2 months), incremental costs of £145,531 and 2.19 incremental QALYs gained, with the ICER increasing to £66,344 per QALY gained for the dinutuximab regimen compared with isotretinoin alone. The company also doubled the administration costs for dinutuximab from £13,784 to £28,399, which increased the ICER to £41,959 per QALY gained.

Evidence Review Group comments

3.16 The ERG noted that the Committee for Medicinal Products for Human Use was aware that the stopping criteria had not been met at the time that recruitment to ANBL0032 stopped. The company explained in its response to NICE's clarification questions that the trial should not have been stopped. The ERG expressed concern that the criteria for stopping had not been reached and commented that if recruitment had continued, the efficacy results may have been different. The ERG also commented that the analyses presented by the company may have overestimated the treatment effect and the results were not adjusted for the early stopping. Although the company explained in its factual accuracy check of the ERG report that each sequential interim analysis was adjusted

according to the protocol for ANBL0032, it did not clarify whether the final analysis was adjusted for early stopping.

3.17 The ERG commented that the company's main analysis was based on the data available after trial recruitment was stopped (January 2009, as reported in Yu 2010). Kaplan–Meier curves and survival estimates 2 years after randomisation were reported for these data. The ERG reviewed the company's data available after 2009 and the company's updated analysis from March 2014. Although the 2009 data represented the primary analysis of the pivotal trial, the ERG noted that the Children's Oncology Group and National Cancer Institute amended the protocol to include a later analysis because the overall survival data in the primary analysis were not considered mature enough. The ERG noted that its clinical advisers also considered 5-year outcomes to be more appropriate, therefore the 2014 analyses would be the most important results for the Committee to consider. The ERG stated that because the analysis from March 2014 included the longest and most complete follow-up data from ANBL0032, the company's submission should have been based on this analysis. It considered that the March 2014 analysis was the most important even taking into account that these data were analysed after randomisation was broken and that because recruitment stopped, the trial was not fully powered to detect the desired treatment effect.

3.18 In its exploratory analyses, the ERG used the Kaplan–Meier survival curves for the 2009, 2012 and 2014 data from the ANBL0032 study presented by the company to reconstruct the hazard ratios for event-free survival and overall survival at years 1 to 5 using methods proposed by Guyot et al. (2012) to check the proportional hazards assumption. The ERG noted that the survival curves for event-free and overall survival for ANBL0032 suggested that approximately 50% of patients are disease free regardless of

their treatment. The ERG fitted various parametric models to the Kaplan–Meier curves for event-free survival and overall survival, with the Weibull cure model representing the best fit for both. The results of the ERG's exploratory analysis showed that for event-free survival, 47% of patients were cured in both arms of the study. This suggested that dinutuximab does not prevent disease progression. However, for overall survival, the proportion of patients cured was 66% in the dinutuximab arm and 48.8% in the isotretinoin arm, suggesting that the dinutuximab regimen delays and possibly prevents mortality.

3.19 The ERG noted that overall the company's model structure was appropriate. The ERG commented that the patient population included in the model did not include patients with evidence of biopsy-proven persistent disease after autologous stem cell transplant and radiotherapy. The ERG noted that people with persistent disease after autologous stem cell transplant and radiotherapy benefitted less from the dinutuximab regimen than those who did not have persistent disease. The ERG stated that excluding this group could possibly lead to a treatment effect in favour of the dinutuximab regimen, which would increase the uncertainty of the economic results.

3.20 The ERG commented on the lifetime time horizon chosen by the company. This assumed that the dinutuximab regimen compared with isotretinoin would result in event-free and overall survival differences that would persist for the rest of the patient's lifetime. The ERG noted that using a lifetime time horizon is only reasonable if the differences in survival are expected to be maintained over a lifetime.

3.21 The ERG also commented on the alternative discount rate of 1.5% used by the company in its scenario analysis. The ERG stated that

the evidence from ANBL0032 suggested that the dinutuximab regimen delays rather than prevents cancer-related events according to the longer term event-free survival evidence presented by the company. Therefore, it was questionable whether this exception applied to dinutuximab.

3.22 The ERG noted that the company's base-case cost-effectiveness analysis was based on the primary 2-year efficacy analysis (June 2009) from ANBL0032, although later data analyses were available. The ERG considered that the updated survival data from ANBL0032 (March 2014 analysis) provided the most relevant estimates of event-free and overall survival for assessing cost effectiveness (see section 3.17).

3.23 The ERG expressed concern that the company's cost-effectiveness results relied on the assumption that the event-free cohort is 'cured' at 5 years (the cure threshold). The ERG noted that the company justified this based on information from the Children's Oncology Group neuroblastoma website, which states that relapses more than 5 years after completing therapy are rare. However, the ERG's clinical advisers suggested that the long-term benefits of immunotherapy are uncertain. Additionally, the ERG noted that the 2014 analysis of ANBL0032 suggested that further events do occur in the dinutuximab arm of the trial after 5 years. This was because the observed data for both event-free and overall survival in the 2014 analysis with dinutuximab and isotretinoin appeared to converge between 6.5 and 11 years. Therefore, the ERG considered that a longer cure threshold of 10 years would be more appropriate.

3.24 The ERG noted that the company tried to apply parametric models to the Kaplan–Meier survival curves from the 2009 analysis of ANBL0032 to reflect the expected survival of patients over a

lifetime time horizon. Because the parametric model predictions were lower than the company expected, it did not use parametric models to reflect the period after the cure threshold of 5 years. The ERG noted that the 2014 analysis of ANBL0032 provided Kaplan–Meier curves for a further 5 years. Therefore, the ERG considered it unnecessary to apply parametric modelling because the data were not extrapolated beyond the trial period.

3.25 The ERG noted that the company assumed that patients in the stable health state at 5 years have the same survival rate as the general population. The ERG identified evidence from the Childhood Cancer Survivor Study, which found a higher standardised annual mortality ratio of 5.6 (95% confidence interval 4.4 to 6.9) among patients surviving neuroblastoma than for low-risk siblings without cancer. In addition, the ERG found it unlikely that patients who had chemotherapy and significant radiotherapy would return to the same mortality risk as the general population.

3.26 The ERG noted that the mortality risk applied in the model for relapse in the failure health state after the 5-year cure threshold was a monthly probability of death of 5.1%, which seemed high. The ERG expressed concern that applying this monthly probability only to the failure health state created an inconsistency in how mortality after relapse is captured in the model. The effect of this inconsistency persists after the cure threshold because of a different proportion of patients being in the failure health state at 5 years for the dinutuximab regimen compared with isotretinoin.

3.27 The ERG noted that the company used evidence from Portwine et al. (2014) to include a decrement in health-related quality of life of 13% compared with the general population for patients in the stable health state at the cure threshold. The ERG considered this could be an underestimate considering the exposure to radiation and

chemotherapy that patients with high-risk neuroblastoma have had. The ERG noted that an alternative decrement of 31.5% could be calculated from Nathan et al. (2007), a study identified by the company, by mapping the SF-36 health survey values from that study to the EQ-5D health survey. The ERG noted that mapping SF-36 values to EQ-5D has some limitations in that the models tended to produce very low scores for more severe health states. As a result, the ERG stated that it had no strong preference for which decrement is used and that the most likely value would lie between 13% and 31.5%.

3.28 The ERG noted that the company used the same procurement cost for the administration costs for dinutuximab, interleukin-2 and topotecan. The ERG considered there should be a distinction between procurement costing bands and delivery of treatment regimens. The ERG also expected the administration costs of dinutuximab and interleukin-2 to be more than the administration costs for topotecan because of the additional number of days that patients are in hospital during immunotherapy. The ERG estimated the total cost of administration for dinutuximab and interleukin-2 to be £28,399. This was based on the average number of hospital days and NHS reference costs for the delivery of complex chemotherapy (the administration cost applied in the company's base case was £13,784). When the ERG applied this to the company's base case, the ICER for the dinutuximab regimen compared with isotretinoin increased from £37,423 per QALY gained to £41,959 per QALY gained. The ERG also calculated alternative administration costs for dinutuximab and interleukin-2. It used the mean number of hospital days (69) from the ANBL0032 study, the costs for the delivery of complex chemotherapy and the mean costs of hospitalisation for an elective inpatient stay for the treatment of paediatric brain tumours. This increased the

administration costs of dinutuximab and interleukin-2 to £60,377. When the ERG applied this alternative administration cost to the company's base case, the ICER for the dinutuximab regimen compared with isotretinoin increased to £49,254 per QALY gained.

3.29 The ERG expressed concern that the company had used the 2009 analysis of ANBL0032 rather than the 2014 analysis, which the ERG considered more mature. Therefore, the ERG used the 2014 data in its preferred exploratory analyses. The ERG also used the 2014 Kaplan–Meier data without parametric modelling and a cure threshold of 10 years. This was because the evidence for event-free and overall survival suggested that the survival curves for dinutuximab therapy and isotretinoin converge between 6.5 and 11 years. When the Kaplan–Meier survival curve data from the 2014 analysis of ANBL0032 were used with a cure threshold of 5 years, the resulting ICER for the dinutuximab regimen compared with isotretinoin was £70,296 per QALY gained. When the cure threshold was increased from 5 to 10 years, the ICER increased to £99,699 per QALY gained for the dinutuximab regimen compared with isotretinoin. When the ERG applied the discount rate of 1.5% to costs and benefits over the lifetime of the model, its base case decreased to £66,690 per QALY gained.

3.30 The ERG explored the implications of an adjustment to the general population mortality for patients who survived neuroblastoma. The higher standardised annual mortality ratio of 5.6 from the Childhood Cancer Survivor Study increased the ERG's base-case ICER from £99,699 to £105,160 per QALY gained.

3.31 The ERG used evidence from Nathan et al. (2007) suggesting that a 31.5% reduction in health-related quality of life might be appropriate for patients in the stable health state after high-risk neuroblastoma. When the ERG applied the 31.5% reduction to the

ERG's exploratory base case (using the 2014 analysis and a cure threshold of 10 years), the ICER for the dinutuximab regimen compared with isotretinoin increased from £99,699 to £112,051 per QALY gained.

3.32 The ERG applied the increased costs of administration for dinutuximab and interleukin-2 to its preferred exploratory base case (using the 2014 analysis and a cure threshold of 10 years). It used costs for the delivery of complex chemotherapy for an elective inpatient stay for the treatment of brain tumours or cerebral cysts (£28,399). The ICER for the dinutuximab regimen compared with isotretinoin increased from £99,699 to £108,872 per QALY gained. Applying the alternative administration costs for dinutuximab and interleukin-2 using costs for the delivery of complex chemotherapy for an elective inpatient stay for the treatment of paediatric brain tumours to the ERG's preferred exploratory base case, the ICER increased from £99,699 to £128,378 per QALY gained.

3.33 The ERG noted that the drug costs used by the company in the model were based on the number of vials needed for an average body surface area of 0.65 metre^2. The ERG noted that 4.8% of patients in ANBL0032 had a body surface area greater than 1 metre^2. The ERG calculated that there would be greater vial wastage and additional costs for patients with a body surface area greater than 1 metre^2. When the ERG applied a weighted average of body surface area to its preferred assumptions, the ICER increased to £103,667 per QALY gained.

3.34 For the alternative assumptions, the ERG's base-case ICER ranged from £99,699 to £128,378 per QALY gained. However, the ERG's ICER for dinutuximab compared with isotretinoin increased to £139,612 per QALY gained (1.97 incremental life years gained [that is, 23.6 months], incremental costs £204,032 and 1.46

incremental QALYs gained) if the following alternative assumptions were considered together:

- using a standardised mortality ratio of 5.6 for patients who survived neuroblastoma
- adjusting the administration cost of dinutuximab
- using a weighted average of body surface area above and below 1 metre^2.

Full details of all the evidence are in the Committee papers.

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of dinutuximab, having considered evidence on the nature of high-risk neuroblastoma and the value placed on the benefits of dinutuximab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.1 The Committee discussed the impact of high-risk neuroblastoma on patients and their families and carers. The patient experts stated that high-risk neuroblastoma had a significant impact on children and young people and their families and carers. The Committee heard from patient experts that patients with high-risk neuroblastoma, in addition to the discomfort and pain caused by the disease, experience anxiety and fears about their illness and treatment. The Committee understood from the patient expert submissions received that patients receive treatments for high-risk neuroblastoma for up to a year and sometimes longer. It noted that treatment can involve many hospital visits and stays causing disruption to school, work and family life. The Committee

understood from the patient submissions received that parents and carers also experience anxiety, emotional distress, disruption to their working life and income as well as strain on their relationships. It also heard from the clinical and patient experts that the effect of a child's death has a significant impact on family members' health-related quality of life. The Committee concluded that high-risk neuroblastoma places a significant burden on patients and their families and carers.

4.2 The Committee considered current clinical practice in the UK for treating high-risk neuroblastoma. It understood that maintenance therapy with isotretinoin is the standard of care in the UK for patients with high-risk neuroblastoma who have received induction chemotherapy followed by surgery (if appropriate), myeloablative therapy and autologous stem cell transplant. The Committee heard from patient experts that these treatments and procedures are painful and debilitating with severe and long-lasting side effects (including hearing loss, organ dysfunction, sterility, growth inhibition, early onset puberty, permanent disability, and secondary malignancies). The Committee heard from the clinical and patient experts that the main aim of treatment at present is to extend event-free survival, but that ultimately what is needed is a cure. The patient experts stated that there are limited options for children and young people with high-risk neuroblastoma and that they urgently need new treatments. The Committee heard from clinical experts that although most patients with high-risk neuroblastoma in the UK are enrolled in the SIOPEN trial which is investigating APN311 (a monoclonal antibody produced in Chinese hamster ovary cells expressing the same gene used to produce dinutuximab), this cannot be considered standard practice. The Committee concluded that isotretinoin is the current standard of care in the UK for the maintenance treatment of high-risk neuroblastoma following

induction chemotherapy and consolidation therapy, but that that the development and availability of new treatment options is very important to patients and their families and carers.

4.3 The Committee considered the company's evidence on the ANBL0032 trial. The Committee noted that this trial was stopped early for ethical reasons. This was because the safety monitoring committee decided that the pre-defined criteria for superiority of the dinutuximab regimen over isotretinoin, as measured by event-free survival, had been met. The Committee also noted that when the data were analysed in 2009, it became clear that the pre-defined criteria had not been met. This concerned the Committee, because stopping a trial for benefit before it has met its primary end point can lead to overestimation of the treatment effect. The Committee also noted that there were data errors and differences between the data sets of January and June 2009, although the company stated that analysis of the results showed similar improvements in event-free survival. It noted that the 2009 overall survival data were not considered mature enough by the Children's Oncology Group and National Cancer Institute and that the protocol was amended to include a later analysis. The Committee noted that follow-up data analyses (June 2012 and March 2014) were available and the company confirmed that the overall survival efficacy analysis of the March 2014 data was requested by the European Medicines Agency. The Committee stated that it preferred longer term data, particularly when patients with the disease have a life expectancy of more than several years. The Committee concluded that the longer term data and the most recent analysis (March 2014) were the most robust data available on which to determine the clinical efficacy of dinutuximab.

4.4 The Committee reviewed the ANBL0032 data (March 2014 analysis) and the Kaplan–Meier curves reconstructed by the ERG

(see section 3.18) to evaluate the clinical efficacy of dinutuximab plus interleukin-2 and granulocyte-macrophage colony-stimulating factor (GM-CSF), compared with standard therapy with isotretinoin alone. The Committee noted that for both the event-free and overall survival data, the curves converge between 6.5 and 11 years. The Committee understood that these longer term data showed that for event-free survival, 47% of patients were cured in both arms of the study, suggesting that the dinutuximab regimen delayed but did not prevent cancer-related events. For overall survival, the data showed that in the dinutuximab regimen arm the proportion of patients cured was 66% and 48.8% in the isotretinoin arm, suggesting that the dinutuximab regimen can delay and possibly prevent mortality. The Committee noted that the trial randomisation should not have been stopped in 2009 because the stopping criteria had not been reached and that because recruitment stopped, the trial was not fully powered to detect the desired treatment effect. The Committee also noted that that the company had planned to evaluate overall survival using a gate-keeping approach (whereby it would not be estimated without first detecting a statistically significant difference in the primary outcome measure, event free survival). The Committee concluded that the dinutuximab regimen does not appear to prevent relapse and although it may be associated with an overall survival benefit, the size of the overall survival benefit is uncertain.

4.5 The Committee considered the evidence presented on the subgroup of patients in ANBL0032 who had biopsy-proven residual disease after autologous stem cell transplant. The Committee noted that this subgroup was small and was not randomised; all patients had the dinutuximab regimen. The Committee was aware that the results for this subgroup were not favourable compared with historical controls, but noted that these types of comparisons

should be viewed with caution. The Committee heard from the company and the clinical experts that it was likely that a proportion of patients who were randomised in the trial would have residual disease, which could have been biopsied if the tumour was amenable and the clinician had chosen to do a biopsy. The Committee concluded there was potentially some overlap between those patients with biopsy-proven residual disease and a proportion of the randomised trial patients with residual disease after autologous stem cell transplant who did not have a biopsy. The Committee noted that the European Medicines Agency stated in the Assessment Report for dinutuximab that as the results in patients with persistent disease were not considered convincing, those patients are not included in the indication. However, it further concluded that it was not possible to draw conclusions about the size of the treatment effect in these groups.

4.6 The Committee considered the adverse reactions seen with the dinutuximab regimen. The Committee heard from the clinical and patient experts that dinutuximab was associated with severe nerve pain that has to be treated with strong analgesics such as morphine, but that the pain relieved as soon as the dinutuximab infusion was stopped. It also noted from the patient expert submissions that capillary leak syndrome (where fluid accumulates inside the body) can be dangerous if it occurs at the site of major organs, such as heart or lungs. The Committee heard from the clinical experts that most adverse reactions were self-limiting and that although some were severe, they were generally manageable. The Committee concluded that the adverse reactions during treatment were very severe (as reflected in the utility values of 0 applied by the company in the economic model), and that the effects stopped when treatment ended.

4.7 The Committee discussed the availability and cost of GM-CSF, noting that it was an integral part of the dinutuximab regimen. It was aware that GM-CSF does not have a marketing authorisation in the UK and is not generally marketed in Europe. The Committee heard from the company that it had arranged supplies of GM-CSF through a third party distributor and that further supplies would be made available in this way. In its submission, the company estimated the price of GM-CSF based on the US price converted into pounds sterling. The Committee noted that the estimated cost of GM-CSF is a small proportion of the total cost of the dinutuximab regimen. It noted that if GM-CSF was available at a similar cost to that estimated by the company, the cost-effectiveness estimates would likely be insensitive to small fluctuations in the GM-CSF price. The Committee concluded that no formal arrangement has been made between the company and the supplier of GM-CSF, and it remained concerned about its cost and supply.

Cost effectiveness

4.8 The Committee considered the company's model comparing the dinutuximab regimen with isotretinoin alone in patients aged 12 months to 17 years with high-risk neuroblastoma who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and autologous stem cell transplantation. It noted that the model was based on a partitioned survival approach (see section 3.7), which took into account the ongoing risks that vary over time. The Committee was aware that this approach is commonly used for evaluating cancer treatments. The Committee concluded that the company's model was generally appropriate.

4.9 The Committee considered the company's decision to use the 2009 analysis of ANBL0032 to form its base-case economic analysis.

The Committee noted that the company's deterministic base-case incremental cost-effectiveness ratio (ICER) for the dinutuximab regimen compared with isotretinoin in people with high-risk neuroblastoma was £37,400 per quality-adjusted life year (QALY) gained. It also noted that in the company's scenario analysis using the 2014 analysis, the ICER increased to £66,300 per QALY gained. The Committee had previously concluded that the most appropriate analysis of ANBL0032 was the March 2014 analysis (see section 4.4), which incorporated the long-term follow-up results from the trial. It also concluded that the 2014 analysis should be the basis for the economic modelling of the dinutuximab regimen compared with isotretinoin.

4.10 The Committee considered the company's choice of 5 years as the cure threshold in the model when the data from ANBL0032 were no longer used. The company assumed that at 5 years, people in the stable health state are considered cured and their health follows that of the general population, taking into account the morbidity associated with surviving neuroblastoma. The Committee noted that the ERG expressed concern at the choice of 5 years because the longer term data from the 2014 analysis showed that events continued to occur beyond year 5. It also noted that the ERG explored the impact of using 10 years as the cure threshold in its analyses. The Committee heard from the patient experts that it was generally accepted that people who survived neuroblastoma for 5 years after treatment could expect to live event-free. However, the Committee heard from the clinical experts that although a relapse after year 5 was rare, it could occur. The clinical experts also stated that relapse after 5 years appears to be increasing, especially relapse affecting the central nervous system. This is perhaps because of disease-modifying immunotherapy treatments such as the dinutuximab regimen that may delay disease

progression. The Committee agreed that the evidence showed that there were further events in ANBL0032 after 5 years, especially in the immunotherapy arm. It also agreed that it was implausible that there would be no events after 5 years, as modelled by the company. The Committee concluded that a cure threshold of 10 years as applied by the ERG was more appropriate than the 5 years used by the company in the cost-effective analysis (see section 3.29).

4.11 The Committee considered the reduction in health-related quality of life applied in the company's model to the stable health state after 5 years. It noted that health-related quality of life was not collected in the ANBL0032 study, and that the company applied a 13% reduction to the general population health utility estimate, based on evidence from Portwine et al. (2014) to reflect potential morbidity in this health state after 5 years. This study was chosen because it included patients with neuroblastoma and had the largest number of patients (n=99) of the studies the company had found. As an alternative the ERG calculated a decrement in utility of 31.5% relative to the general population, using the same approach as the company, based on a study by Nathan et al. (2007). The Committee heard from the clinical experts that although patients who survive neuroblastoma will have a decrement in quality of life compared with the general population, a reduction of 31.5% seemed excessive. The clinical experts also pointed out that the Nathan et al. study included patients with low-risk neuroblastoma, which unexpectedly, can result in more long-term disabilities such as paralysis, and that this does not necessarily represent patients who survive high-risk neuroblastoma. The patient expert commented that quality of life can be well maintained in patients who survive neuroblastoma. The Committee heard from the clinical and patient experts that the utility decrement of 13% applied by the

company in its base case seemed the most reasonable estimate and could possibly be smaller for patients who survive neuroblastoma in the stable health state. The Committee concluded that there was considerable uncertainty about accurately determining the size of the decrement in health-related quality of life, but having heard from the experts, the Committee agreed that the 13% decrement in health-related quality of life applied by the company was a reasonable assumption.

4.12 The Committee considered the mortality rates applied in the model by the company. The Committee noted that the company applied a monthly mortality rate of 5.1% to the failure health state after 5 years in the model. The Committee heard from the clinical experts that for all patients whose neuroblastoma had relapsed to have died within 20 months was not in line with their experience and the monthly mortality rate applied in the model was too high. The Committee was also aware that the company applied a general population mortality rate to the stable health state after 5 years. The ERG explained that this creates an inconsistency in how mortality is captured in the model, resulting in a different treatment effect on mortality after the trial period. The Committee noted that the ERG identified an annual standardised mortality ratio of 5.6 from the Childhood Cancer Survivor study for patients surviving neuroblastoma compared with low-risk siblings without cancer and explored the impact of applying it to the stable and failure health states in the model (see section 3.23). The Committee concluded that the mortality rate applied by the company to the failure health state was too high, but that applying the general population mortality rate to the stable health state was too low. Therefore, using an annual standardised mortality rate for both health states as applied by the ERG was a reasonable approach.

4.13 The Committee discussed the administration costs of dinutuximab and interleukin-2 applied by the company in the model. The company applied the same costs to dinutuximab, interleukin-2 and topotecan. The Committee heard from the clinical experts that they would have expected the administration costs for dinutuximab and interleukin-2 to be higher because of the number of additional days that patients are hospitalised when having the dinutuximab regimen. The Committee noted that when the ERG adjusted the administration costs of dinutuximab and interleukin-2 from £13,800 to £28,400 (based on the average number of hospital days [69] from the ANBL0032 study using the cost of an elective inpatient stay for treating brain tumours or cerebral cysts with the highest complication and comorbidity level and NHS reference costs for the delivery of complex chemotherapy) the ICER increased from the company's base case of £37,400 per QALY gained to £42,000 per QALY gained. The ERG did an additional scenario analysis using the average number of hospital days (69) from the ANBL0032 study and the cost of hospitalisation for an elective inpatient stay for treating paediatric brain tumours, which increased the administration costs of dinutuximab and interleukin-2 to £60,400. This increased the company's base-case ICER to £49,300 per QALY gained. The clinical experts also highlighted that using the average number of hospital days from the ANBL0032 study (69 days) may also have underestimated the number of days a patient with neuroblastoma would be hospitalised when having treatment with the dinutuximab regimen. The Committee noted there was no specific code available for the maintenance treatment of high-risk neuroblastoma. The Committee accepted that without a specific code, the cost of an elective inpatient stay for treating paediatric brain tumours could be considered the most applicable for patients having dinutuximab. However, considering the clinical experts' concern that average number of hospital days from the ANBL0032

study seemed to underestimate the number of days a patient with high-risk neuroblastoma would be hospitalised, the Committee concluded that the costs used in the ERG's scenario analysis may still underestimate the administration costs of the dinutuximab regimen.

4.14 The Committee considered the company's assumption about body surface area used in the model to calculate the number of vials used during a treatment course. The Committee heard from the ERG that because dosage is based on body surface area, some patients needed more than 1 vial of dinutuximab during the infusion. The Committee heard from the company that although classed as single use, 1 vial could be used to prepare the infusion, and the remaining dinutuximab in the vial could be used for the next infusion. The Committee was aware that 4.8% of patients included in ANBL0032 had a body surface area over 1 metre^2. The Committee noted that the ERG's exploratory analyses had applied a weighted average for body surface area to account for the additional vials required for patients with a body surface area over 1 metre^2. The Committee concluded that this was the right approach to adjust the cost-effectiveness estimates to account for the extra vials needed to treat patients with a body surface area greater than 1 metre^2.

4.15 The Committee considered the ERG's exploratory analyses, which used the March 2014 data from ANBL0032. These analyses used the Kaplan–Meier data directly to estimate event-free and overall survival, with a cure threshold of 10 years. The Committee accepted that using the Kaplan–Meier data directly is the best approach because it reflects the actual treatment effect seen in the trial. The Committee noted that when these changes were made to the base case, the ERG's base-case exploratory ICER for the dinutuximab regimen compared with isotretinoin increased to

£99,700 per QALY gained (the company's base case was £37,400 per QALY gained). The Committee also noted that when the ERG applied increased administration costs for dinutuximab (of £60,400) to its exploratory base-case, the ICER increased to £128,400 per QALY gained. It further noted that the ERG's exploratory base-case ICER increased to £105,200 per QALY gained when a standardised mortality rate was applied for both the stable and failure health states after 5 years in the model. When the ERG used a weighted average for body surface area in addition to the exploratory base-case assumptions, the ICER increased to £103,700 per QALY gained. The Committee noted that when all these assumptions were applied, together with the company's base-case utility decrement (13%) for patients surviving neuroblastoma, the ICER for the dinutuximab regimen compared with isotretinoin increased to £139,600 per QALY gained. It concluded that of the ICERs it was presented, this was the most likely cost-effectiveness estimate.

4.16 The Committee discussed whether a non-reference-case discount rate of 1.5% should be applied to the costs and benefits. The Committee noted that NICE's guide to the methods of technology appraisal states:

'In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered.

A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of

the evidence presented, the long-term health benefits are likely to be achieved. Further, the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs'.

4.17 For dinutuximab, the Committee noted that the evidence from ANBL0032 suggested that half the patients will not have a relapse regardless of treatment with the dinutuximab regimen or isotretinoin alone. The Committee also noted that there was no evidence from the trial to suggest there were differences in health-related quality of life between patients who had the dinutuximab regimen and those who had isotretinoin alone. The Committee noted the evidence and heard from the experts that patients who recover from neuroblastoma never return to full health. However, the clinical experts stated that these patients could be considered to have similar health-related quality of life to that of the general population. It was clear to the Committee that although there is debate among clinical experts about what size of decrement in health-related quality of life should be applied for patients surviving neuroblastoma, the Committee did not expect that the health-related quality of life of patients in the stable health state would be the same as the general population. The Committee noted that the Kaplan–Meier curves in ANBL0032 showed a levelling off in event-free survival in both arms at approximately 8 years and at approximately 10 years for overall survival. The ERG's interpretation of this, which was shared by the Committee and the clinical experts, was that approximately half the patients can be considered cured regardless of the treatment they have and they will survive long term. The ERG's reconstructed Kaplan-Meier data also showed that for event-free survival, the cure rate was 47% in both arms, showing that immunotherapy delays, but does not prevent, relapse. The Committee noted that ANBL0032 is ongoing

but considered that, based on the 2014 Kaplan-Meier curves, any survival benefit is likely to be small and uncertain and only seen in a proportion of those having the dinutuximab regimen. The Committee concluded that the non-reference case discount rate should not apply because the dinutuximab regimen does not cure neuroblastoma, but rather prevents relapse of the disease and potentially offers some overall survival benefit.

4.18 The Committee considered whether the dinutuximab regimen could be considered an innovative treatment. The Committee heard from the company that this was the first immunotherapy licensed for the maintenance treatment of high-risk neuroblastoma. The Committee listened to the history of dinutuximab as a maintenance treatment for neuroblastoma from the patient experts. The Committee heard that adding cytokines to dinutuximab for treating high-risk neuroblastoma occurred because of an apparent lack of clinical benefit of dinutuximab when used alone. The Committee heard from the patient and clinical experts that it is not possible to determine the relative contributions of each component of the dinutuximab regimen to event-free and overall survival outcomes. The Committee noted that the European Medicines Agency stated in the Assessment Report for dinutuximab that the contribution of each component of the dinutuximab regimen to the efficacy results is difficult to appreciate. The Committee concluded that the dinutuximab regimen represents a novel approach as a maintenance therapy for treating high-risk neuroblastoma, but the evidence of the health gains specifically from dinutuximab (as opposed to the other drugs included in the regimen) remains uncertain.

4.19 The Committee considered whether there were any health-related benefits that were not captured in the economic analysis. The Committee 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 are uncaptured health-related benefits such as the 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 effect of bereavement on families. The Committee also acknowledged the severity of the disease and the importance of generating health benefits for this patient population. The Committee was prepared to consider accepting a higher ICER for a patient population of children and young adults, as well as any other uncaptured health-related benefits that the dinutuximab regimen might offer patients with high-risk neuroblastoma and their families. However, it was not presented with any data to show distinct and substantial uncaptured health-related benefits. The Committee also recognised the high unmet clinical need for effective new treatments to treat minimal residual disease and prevent relapse of neuroblastoma. The Committee was confident that there were health-related benefits that were not captured in the company's model, but because it had not been presented with any data, it could not form an opinion about the extent of the impact those data might have on the cost-effectiveness estimates.

4.20 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met.

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.

- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.21 The Committee considered the criterion for extension to life. The Committee noted that in the company's base case comparing the dinutuximab regimen with isotretinoin alone, 2.85 life years were gained (approximately 34.2 months). Using the Committee's preferred assumptions, 1.97 life years (approximately 23.6 months) were gained for the dinutuximab regimen compared with isotretinoin alone. The Committee concluded that the dinutuximab regimen appeared to produce an additional survival advantage of at least 3 months.

4.22 The Committee considered the criterion for small patient populations. The Committee noted the company's estimate of approximately 54 people in England and Wales who are expected to be eligible for the dinutuximab regimen. The Committee concluded that this criterion was met.

4.23 The Committee considered the criterion for short life expectancy. It noted that in the company's submission the median life expectancy for patients with high-risk neuroblastoma was 4 years. The Committee noted that this is double the life expectancy set out in the criterion. The Committee concluded that for most patients with high-risk neuroblastoma, dinutuximab does not fulfil the criterion for

short life expectancy. Based on the discussion in sections 4.21, 4.22 and 4.23, the Committee agreed that dinutuximab did not fulfil all the criteria for special consideration under the supplementary advice from NICE.

4.24 The Committee concluded that the dinutuximab regimen may represent a novel approach as a maintenance therapy for treating high-risk neuroblastoma. However, there is no evidence of any dinutuximab regimen-related event free survival advantage compared to isotretinoin alone and the overall survival benefit relative to standard UK clinical practice remains uncertain. Furthermore, the Committee agreed that the most plausible ICER for the dinutuximab regimen compared to dinutuximab based on the evidence available was £139,600 per QALY gained. The Committee considered there may be a case for accepting a higher ICER for a patient population of children and young adults to account for the uncaptured health-related benefits of treatment. However, the ICER was too high to allow the Committee to recommend the dinutuximab regimen, even when taking into account other aspects of health-related quality of life not adequately captured in the QALY. The Committee concluded that dinutuximab does not represent a cost-effective use of NHS resources and that it should not be recommended for treating high-risk neuroblastoma in patients between12 months and 17 years, whose disease has at least partially responded to induction chemotherapy, followed by myeloablative therapy and autologous stem cell transplant.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Dinutuximab for treating high-risk neuroblastoma	Section
Key conclusion		
Dinutuximab, in combination with granulocyte-macrophage colony-stimulating factor, interleukin-2 and isotretinoin, is not recommended within its marketing authorisation, for treating high-risk neuroblastoma in children and young people between 12 months and 17 years whose disease has at least partially responded to induction chemotherapy, followed by myeloablative therapy and autologous stem cell transplant.		1.1
Current practice		
Clinical need of patients, including the availability of alternative treatments	High-risk neuroblastoma places a significant burden on patients and their families and carers, and that the availability of new treatment options is very important to them. The development and availability of new treatment options is very important to patients and their families and carers	4.3 4.2

The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee concluded that the dinutuximab regimen does not appear to prevent relapse and although it may be associated with an overall survival benefit, the size of the overall survival benefit is uncertain. The dinutuximab regimen represents a novel approach as a maintenance therapy for treating high-risk neuroblastoma, but the evidence of the health gains specifically from dinutuximab (as opposed to the other drugs included in the regimen) remains uncertain.	4.4 4.18
What is the position of the treatment in the pathway of care for the condition?	Dinutuximab was not recommended for treating high-risk neuroblastoma in patients between 12 months and 17 years, whose disease has at least partially responded to induction chemotherapy, before myeloablative therapy and autologous stem cell transplant.	4.244
Adverse reactions	Adverse reactions with dinutuximab could be severe, but the effects stopped when treatment ended.	4.6
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The company's clinical effectiveness data were based on the ANBL0032 trial, an international, multicentre, partially randomised study. This trial was stopped early for ethical reasons because the safety monitoring committee decided that the pre-defined	4.3

	criteria for superiority of the dinutuximab regimen over isotretinoin, as measured by event-free survival, had been met. The Committee also noted that when the data were analysed in 2009, it became clear that the pre-defined criteria had not been met. This concerned the Committee, because stopping a trial for benefit before it has met its primary end point can lead to overestimation of the treatment effect. Follow-up analyses were done in March 2014. The Committee concluded that the longer term data and the most recent analysis were the most robust data available on which to determine the clinical efficacy of dinutuximab.	
Relevance to general clinical practice in the NHS	n/a	
Uncertainties generated by the evidence	The dinutuximab regimen does not appear to prevent relapse and although it may be associated with an overall survival benefit, the size of the overall survival benefit is uncertain. No formal arrangement has been made between the company and the provider of granulocyte-macrophage colony-stimulating factor (GM-CSF), and the Committee remained concerned about the cost and supply of GM-CSF.	4.4 4.7

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	Although the company presented evidence for a subgroup of patients in ANBL0032 who had biopsy-proven residual disease after autologous stem cell transplant, it was not possible for the Committee to draw any conclusions about the size of the treatment effect in these groups.	4.5
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The dinutuximab regimen does not appear to prevent relapse and although it may be associated with an overall survival benefit, the size of that benefit is uncertain.	4.4
Evidence for cost effectiveness		
Availability and nature of evidence	The company used the 2009 analysis of ANBL0032 to form its base-case economic model. The Committee concluded that the most appropriate analysis of ANBL0032 was the March 2014 analysis, which incorporated the long-term follow-up results from the trial. It also concluded that the 2014 analysis should be the basis for the economic modelling of the dinutuximab regimen compared with isotretinoin.	4.9
Uncertainties around and plausibility of assumptions and inputs in the economic model	The company assumed that at 5 years in the model, people in the stable health state are considered cured and their health follows that of the general population. The Committee heard from the clinical experts that although a relapse after year 5 was rare, it could occur	4.10

	and appears to be increasing. The most recent results from ANBL0032 showed that further events occurred in the immunotherapy arm after 5 years. The Committee agreed that it was implausible that no events would occur after 5 years as modelled by the company. Therefore, a longer cure threshold of 10 years as applied by the ERG was more appropriate.	
	The mortality rate applied by the company to the failure health state was too high, and the general population mortality rate applied to the stable health state was too low. Therefore, using an annual standardised mortality rate for both health states as applied by the ERG was a reasonable approach.	4.12
	The administration costs applied by the company for dinutuximab and interleukin-2, which were based on the administration costs for topotecan, were too low. Although the ERG calculated higher administration costs based on the average number of hospital days and the cost of hospitalisation for an elective inpatient stay for treating paediatric brain tumours and NHS reference costs for the delivery of complex chemotherapy, the Committee remained concerned that these administration costs might underestimate the costs of administering the dinutuximab regimen.	4.13 4.16, 4.17
	It concluded that the non-reference case	

	discount rate should not apply because the dinutuximab regimen does not cure neuroblastoma, but rather prevents relapse of the disease and potentially offers some overall survival benefit.	
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The company applied a 13% reduction in health-related quality of life to reflect potential morbidity in the stable health state after 5 years, based on evidence from Portwine et al. (2014). This study was chosen because it included patients with neuroblastoma and had the largest number of patients (n=99) of the studies it had found. The Committee agreed that the 13% decrement in health-related quality of life applied by the company was a reasonable assumption. The company applied a monthly mortality rate of 5.1% to the failure health state and a general population mortality rate to the stable health state after 5 years in the model. The Committee concluded that the mortality rate applied by the company to the failure health state was too high, but that applying the general population mortality rate to the stable health state was too low. Therefore, using an annual standardised mortality rate for both health states as applied by the ERG was a reasonable approach. The Committee was confident that there were health-related benefits that were not captured	4.11 4.12 4.19

	in the company's model, such as reduced quality of life because of the effect of stress and depression caused by the disease on patients and families, as well as the effect of bereavement on families. However, because it had not been presented with any data, it could not form an opinion about the extent of the impact those data might have on the cost-effectiveness estimates.	
Are there specific groups of people for whom the technology is particularly cost effective?	n/a	
What are the key drivers of cost effectiveness?	The key drivers of cost effectiveness are the choice of analysis (2009 or 2014) from the ANBL0032 study, the discount rate applied, and the administration costs used for dinutuximab and interleukin-2.	4.13, 4.16,
Most likely cost-effectiveness estimate (given as an ICER)	The Committee noted that when its preferred assumptions were applied, the incremental cos-effectiveness ratio (ICER) increased to £139,600 per quality-adjusted life year (QALY) gained, which the Committee concluded was the most likely cost-effectiveness estimate.	4.15
Additional factors taken into account		

End-of-life considerations	The Committee concluded that for most patients with high-risk neuroblastoma, dinutuximab does not fulfil the criterion for short life expectancy. Therefore, it does not fulfil all the criteria for special consideration under the supplementary advice from NICE.	4.23
Equalities considerations and social value judgements	No equality issues were raised during the appraisal.	

5 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the NICE website.

Published

- Improving outcomes in children and young people with cancer. Cancer service guideline (2005). Review proposal date: June 2016.
- Children and young people with cancer. Quality standard 55 (2014). Review proposal date to be confirmed.

6 Proposed date for review of guidance

6.1 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
November 2015

7 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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.

Professor Gary McVeigh (Chair)
Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr Lindsay Smith (Vice Chair)
GP, West Coker Surgery, Somerset

Dr Andrew Black
GP, Mortimer Medical Practice, Herefordshire

Dr Matthew Bradley

Vice President, Value Evidence and Outcomes, GlaxoSmithKline

Ms Tracey Cole
Lay Member

Dr Ian Davidson

Lecturer in Rehabilitation, University of Manchester

Professor Simon Dixon

Professor of Health Economics, University of Sheffield

Susan Dutton

Senior Medical Statistician, Oxford Clinical Trials Research Unit

Dr Susan Griffin

Research Fellow, Centre for Health Economics, University of York

Professor Carol Haigh

Professor in Nursing, Manchester Metropolitan University

Professor John Henderson

Professor of Paediatric Respiratory Medicine, University of Bristol and Bristol Royal Hospital for Children

Dr Warren Linley

Independent Pharmacist and Health Economist

Dr Malcolm Oswald

Lay Member

Professor Femi Oyebode

Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health

Dr Paul Parvulescu

Consultant in Public Health Medicine, Liverpool County Council

Dr Mohit Sharma

Consultant in Public Health, Public Health England

Dr Murray Smith

Associate Professor in Social Research in Medicines and Health, University of Nottingham

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.

Richard Diaz

Technical Lead

Fay McCracken

Technical Adviser

Kate Moore

Project Manager

8 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by the Centre for Reviews and Dissemination and the Centre for Health Economics Technology Assessment Group, University of York:

- Saramango P, et al. Dinutuximab for treating high-risk neuroblastoma: A Single Technology Appraisal. CRD and CHE Technology Assessment Group, September 2015

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- United Therapeutics Corporation

II. Professional/expert and patient/carer groups:

- Children's Cancer and Leukaemia Group
- Neuroblastoma UK
- Solving Kids Cancer
- Cancer Research UK
- Royal College of Nursing
- Royal College of Paediatrics and Child Health
- Royal College of Pathologists

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland

- Roche
- National Cancer Research Institute
- National Collaborating Centre for Cancer

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on dinutuximab by attending the initial Committee discussion and providing a written statement to the Committee. They are invited to comment on the ACD.

- Dr Martin Elliott, Consultant in Paediatric Oncology, nominated by the National Cancer Research Institute – clinical expert
- Dr Juliet Grey, Associate Professor and Consultant in Paediatric Oncology, nominated by the National Cancer Research Institute – clinical expert
- Mr Nicholas Bird, nominated by Solving Kids Cancer – patient expert
- Mr Stephen Smith, nominated by Neuroblastoma UK – patient expert

E. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- United Therapeutics