NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Dinutuximab for treating high-risk neuroblastoma

1 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 aged 1–17 years whose disease has at least partially responded to induction chemotherapy, myeloablative therapy and autologous stem cell transplant.

1.2 This guidance is not intended to affect the position of patients whose treatment with dinutuximab was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published 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 and/or their parents or carers.

2 The technology

2.1 Dinutuximab (Unituxin, United Therapeutics) is an immunotherapy treatment; 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 that 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 consists of 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) is £6,390 (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 of a complete course when isotretinoin, GM-CSF (using the US list price converted to pounds sterling) and interleukin-2 are included is £135,404. The company has agreed a patient access scheme with the Department of Health. If dinutuximab had been recommended, this scheme would provide a simple discount to the list price of dinutuximab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered

that this patient access scheme would not constitute an excessive administrative burden on the NHS. Costs may vary in different settings because of negotiated procurement discounts.

3 Evidence

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). See the committee papers for full details of the evidence.

Clinical effectiveness

3.1 The company's submission included 1 international, multicentre, partly randomised, event-driven trial (ANBL0032; n=226). This trial 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 was open to 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 had adequate renal, liver, cardiac, pulmonary and central nervous system function. Patients were randomised to the dinutuximab regimen (n=113) or isotretinoin (n=113).

3.2 The Children's Oncology Group and National Cancer Institute originally estimated the trial 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 criterion was 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. The trial randomisation was stopped early in January 2009. According to the company, the trial randomisation 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 (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 at 2 years after randomisation.

3.3 After randomisation stopped 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. Compared with the 2009 analysis, the 2014 analysis suggested that patients having the dinutuximab regimen showed a relatively smaller event-free survival advantage (59.3% and 48.3% respectively; hazard ratio [HR] 0.76. 95% confidence interval [CI] 0.52 to 1.11, p=0.15) and a relatively smaller overall survival advantage (75.1% and 61.0% respectively; HR 0.62, 95%CI 0.40 to 0.96, p=0.03) when compared with isotretinoin. The company stated in its submission that the 2014 analysis was inadequately powered to detect

statistical differences between immunotherapy and standard therapy because 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 (87%) enrolled in ANBL0032 were known: 167 patients had a Curie score of 0 (82 patients had isotretinoin alone and 85 had dinutuximab plus isotretinoin) and 30 patients had a score greater than 0 (15 patients in each group). 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 (in which fluid leaks from blood vessels into neighbouring tissue; 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.

3.9 The company used the 2009 data cut and analyses from ANBL0032 (as reported in Yu et al. 2010) 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 the 2009 data cut and analyses of 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. It 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 treatment failure health state of the model after year 5, the company applied a monthly mortality probability of 5.1%. In this health state, patients had topotecan combination treatment every month until death.

3.11 Because 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 treatment failure health state continued to have a health utility of 0.56, whereas patients in the stable health state were assumed to have similar characteristics to those of the general population. This was 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. The company 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; £1,908). 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 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) and the discount rate used. When the 2014 data and parametric survival curves were 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. When the company used the non-reference discount rate of 1.5% for outcomes only, the ICER was reduced to £48,061 per QALY gained for the dinutuximab regimen compared with isotretinoin alone.

Evidence review group comments

3.15 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 ERG expressed concern that the trial had been stopped although 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 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.

3.16 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 et al. 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 follow-up data 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 the 2014 dataset from ANBL0032 to be more appropriate that is, the outcomes calculated 5 years after randomisation. 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. The ERG stated that the March 2014 analysis of survival and progression was also more appropriate than the 2009 analysis because there were some errors in the 2009 data and the 2009 analysis was inconsistent with later analyses. The ERG stated that there were no concerns about the 2014 analysis being done after randomisation was broken.

3.17 The ERG noted that ANBL0032 was designed to recruit 386 patients to achieve an 80% power of detecting an event-free survival difference of 15% after 3 years, but that recruitment was

stopped early after 226 randomisations. The ERG stated that the 2009 analysis was not fully powered to detect the desired treatment effect. However, because the statistical power of the trial was determined based on the number of events, the 2014 analysis had more power than the 2009 analysis to detect the treatment effect because more events had occurred during follow-up.

3.18 In its exploratory analyses, the ERG used the Kaplan–Meier survival curves for the 2009, 2012 and 2014 data from ANBL0032 presented by the company to reconstruct the hazard ratios for event-free survival and overall survival at years 1 to 5. The ERG used 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.

3.19 The ERG noted that overall the company's model structure was appropriate. 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.

3.20 The ERG also commented on the alternative discount rate of 1.5% used by the company in a 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 alternative rate applied to dinutuximab.

3.21 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 Kaplan–Meier data from ANBL0032 showed that further events occurred in the dinutuximab arm of the trial after 5 years and did not plateau until approximately year 8. Because there were observed events beyond year 5 and these did not appear to continue beyond year 10, the ERG considered that a longer cure threshold of 10 years would be more appropriate.

3.22 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 an additional 5 years of Kaplan–Meier data. Therefore, the ERG considered it unnecessary to apply parametric modelling because the data were not extrapolated beyond the trial period.

3.23 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 that found a higher standardised annual mortality ratio of 5.6 (95% CI 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. Therefore, the ERG explored the effect of applying the standardised annual mortality ratio of 5.6 to the stable health state in the model beyond 5 years.

3.24 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.

3.25 The ERG noted that the company used evidence from Portwine et al. (2014) to include a 13% decrement in health-related quality of life for patients in the stable health state at the cure threshold compared with the general population. 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%.

3.26 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. It also expected the administration costs of dinutuximab and interleukin-2 to be more than the administration costs for topotecan because of the extra 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 ANBL0032, 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.

3.27 The ERG used the reconstructed 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 continue to converge between 6.5 and 11 years. When the 2014 analysis of ANBL0032 was 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.

3.28 The ERG explored the implications of an adjustment to the general population mortality for patients who survived neuroblastoma. When the higher standardised annual mortality ratio of 5.6 from the Childhood Cancer Survivor study was applied to patients who were event free at the cure point of 10 years in the model, it increased the ERG's base-case ICER from £99,699 to £105,160 per QALY gained.

3.29 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 March 2014 Kaplan–Meier data 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.

3.30 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.

3.31 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.

3.32 For the alternative assumptions, the ERG's revisions to the 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 in the progression-free survival health state
- adjusting the administration cost of dinutuximab
- using a weighted average of body surface area above and below 1 metre^2.

When the ERG used a 1.5% discount rate for outcomes and costs, the ERG's ICER for dinutuximab compared with isotretinoin was £98,798 per QALY gained (2.81 incremental life years gained [that is, 33.7 months], £207,980 incremental costs and 2.11 incremental QALYs gained) using the alternative assumptions listed above.

Additional evidence and patient access scheme

3.33 In response to the appraisal consultation document, the company highlighted that the data it had provided to the ERG to calculate the administration cost of dinutuximab were incorrect. The company stated that the mean number of hospital days (69 days) calculated by the ERG was based on hospitalisation data from ANBL0032 for patients with infections and did not represent the mean hospitalisation rates for the administration of dinutuximab regardless of infection status. Therefore, the company presented additional data from ANBL00931, an open-label safety study (n=104) in patients with high-risk neuroblastoma who received the same treatment regimen as administered in ANBL0032. The mean number of hospital days for patients without infection in ANBL00931 was 39 days (±21.3 days). On request, the company updated the calculation of the mean number of hospital days for ANBL0032, which was 35 days per patient in the immunotherapy plus isotretinoin arm of the trial. This confirmed that the mean number of hospital days from ANBL00931 was similar to that seen in ANBL0032. The company also agreed a confidential patient access scheme discount for dinutuximab with the Department of Health.

3.34 The company presented a revised base-case analysis using the updated hospitalisation data from ANBL0032 to calculate the administration cost for dinutuximab. The company also used the less costly hospital code (AA24C £449.92 per day using 2013–14 reference costs) rate for the delivery of complex chemotherapy for an elective inpatient stay for the treatment of brain tumours or cerebral cysts to calculate the administration cost for dinutuximab, rather than the more costly code for the treatment of paediatric brain tumours (PM42A £991.92 per day using 2013–14 reference costs) preferred by the committee and the ERG. It also used a

weighted average of 4.2 vials per treatment course in its revised base case. The company's revised analysis was based on the observed 2014 Kaplan–Meier data, a 5.6 mortality ratio for stable health and a 10-year cure point. The company used a 1.5% discount rate for outcomes and costs in its revised analysis on the basis that there are long-term health benefits associated with dinutuximab treatment in accordance with the guide to the methods of technology appraisal. The company's new base-case ICER for dinutuximab compared with isotretinoin was £84,438 per QALY gained without the patient access scheme discount for dinutuximab. The ICER with the patient access scheme discount applied was lower but it is commercial in confidence.

3.35 The committee was also presented with alternative hospital codes and costs by the clinical experts who had attended the first and second committee meetings. These included a hospital code for an inpatient stay of 1 day or more for paediatric patients with a neoplasm and no other comorbidities (PM43C: £994 per day; reference costs 2013–14) and a code for delivery of complex chemotherapy including prolonged infusion, which was not specific to the paediatric population (SB14Z/SB15Z: £401 for the first day and £328 for the second day; reference costs 2013–14). One clinical expert also provided the average spell income per admission at her local trust (£3,444 per admission in 2014–15). The ERG identified that the code for PM43C was replaced by PM43B in the reference costs for 2016–17, which was now £2,600 per admission up to 7 days (an average of £371 per day) and £288 every additional day.

3.36 The ERG conducted exploratory analyses using alternative hospital codes, including those identified by the clinical experts:

- It used the committee's preferred assumptions and the ERG's preferred hospitalisation code PM42A (using 2013–14 reference costs) for delivery of complex chemotherapy for paediatric brain tumours with length of stay of more than 1 day.
- It corrected the mean hospitalisation rate (using 35 days from ANBL0032).

This resulted in an ICER for dinutuximab compared with isotretinoin of £88,031 per QALY gained without the patient access scheme discount for dinutuximab. The ERG also applied the confidential patient access scheme discount, but the results of those analyses are commercial in confidence. The ERG noted that the changes in hospital days and cost code chosen had little impact on the resulting ICERs because the key driver of cost effectiveness was the price of dinutuximab. In a different scenario analysis, the ERG reduced the cost of hospital administration to £0 and the resulting ICER remained above the range that NICE technology appraisal committees usually considers to be cost effective.

4 Committee discussion

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, 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, have anxiety and fears about their illness and treatment. The committee understood from the patient expert submissions that patients have treatment 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 expert submissions that parents and carers also have 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 death of a child disrupts parents' health-related quality of life and well-being during bereavement and for extended periods over the course of their lives. 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 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 of puberty, permanent disability, and secondary malignancies). The committee heard from the clinical and patient experts that the main aim of treatment 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 most patients with high-risk neuroblastoma in the UK are enrolled in the SIOPEN trial that is investigating APN311 (a monoclonal antibody produced in Chinese hamster ovary cells expressing the same gene used to produce dinutuximab). However, it was aware that APN311 is not currently licensed for treating neuroblastoma and, because its use in a research setting is viewed as use in new and experimental circumstances, the committee agreed that for those reasons APN311 could not be considered established practice. The committee concluded that isotretinoin is established practice in the UK for the maintenance treatment of high-risk neuroblastoma after induction chemotherapy, myeloablative therapy and autologous stem cell transplant, but that the development and availability of new treatment options for neuroblastoma is very important to patients and their families and carers.

4.3 The committee considered the ANBL0032 trial, which it noted was stopped early. 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 understood 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. The committee noted that, for these reasons, the European Medicines Agency considered that the event-free survival results from ANBL0032 should be interpreted with caution.

The committee noted that the Children's Oncology Group and National Cancer Institute did not consider the 2009 overall survival data to be mature enough, and that the protocol was amended to include a later analysis for both event-free and overall survival 2 years after the end of randomisation. 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 that provides additional information on outcomes, particularly when patients with the disease have a life expectancy of more than several years. In response, the company stated that ANBL0032 was not powered to detect events beyond the 3 years planned in the protocol and therefore the 2012 data cut was the most appropriate for the committee to focus upon. However, the committee was aware that the statistical power of a trial was determined based on the number of events, therefore, so long as the required number of events have occurred, it is sufficiently powered to detect a treatment effect even when more events occur on follow-up. 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 results of ANBL0032 from the March 2014 analysis. Using the 2014 data cut, the committee noted that the Kaplan–Meier curves suggested that a higher proportion of patients having dinutuximab could remain event free compared with isotretinoin. The committee noted that the results showed a difference in overall survival between people having dinutuximab and people having isotretinoin, although the trial was not powered to show a statistically significant difference. It also observed that

event-free survival was higher in the dinutuximab group than in the isotretinoin group, although the difference between the 2 groups was not statistically significant. The committee noted that patients randomised to dinutuximab had a relatively smaller event-free survival and overall survival advantage (see section 3.3) at 4 years than those having isotretinoin in the 2014 analysis compared with the 2009 analysis. The committee concluded that a small proportion of patients having the dinutuximab regimen remain event free and that the regimen may be associated with an overall survival benefit, although the size of these benefits is uncertain.

4.5 The committee considered the adverse reactions seen with the dinutuximab regimen. It heard from the clinical and patient experts that dinutuximab infusion is associated with severe nerve pain that needs to be treated with strong analgesics such as morphine, but that the pain is relieved as soon as the infusion is stopped. It also noted from the patient expert submissions that capillary leak syndrome (which was only seen in the dinutuximab arm of the trial) can be dangerous if it occurs in major organs, such as the heart or lungs. The committee accepted the statements from the clinical experts that most adverse reactions were self-limiting and that although some were severe, they were generally manageable, and understood that this was reflected in the utility values of 0 applied by the company in the economic model

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4.6 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 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. The committee noted that the estimated cost of GM-CSF, converted to pounds sterling from the US price, represents a small proportion of the total cost of the dinutuximab regimen. It accepted that, if the cost of GM-CSF for NHS patients remains similar to its cost in the US, small fluctuations in the currency exchange rate would be unlikely to impact the cost-effectiveness estimates. The committee concluded although the company provided some assurances about the availability of GM-CSF, these arrangements would need to be formalised if positive NICE guidance were to be implemented. .

Cost effectiveness

4.7 The committee considered the company's model comparing the dinutuximab regimen with isotretinoin alone in patients of 1–17 years with high-risk neuroblastoma who have partially responded to induction chemotherapy, 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 and concluded that the company's model was generally appropriate.

4.8 The committee considered the company's additional evidence, which used data from the 2014 analysis of ANBL0032 rather than the 2009 data used in the company's original base-case economic analysis. It noted that the incremental cost-effectiveness ratio (ICER) from the company's revised analysis (without the patient access scheme applied and with the error corrected) was £48,900 per quality-adjusted life year (QALY) gained.

4.9 The committee considered the company's initial 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 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 in the dinutuximab arm 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 had received isotretinoin as standard of care and 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, in the era of immunotherapy it could occur. The committee heard from clinicians that relapse beyond 10 years is extremely unlikely. It 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. The committee noted that the company provided revised analyses using the 10-year cure threshold. It concluded that a cure threshold of 10 years, as used by the company in its revised base-case analyses, was more appropriate than the 5 years used in the company's original base case.

4.10 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 data were not collected in ANBL0032 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. Portwine et al. 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 lower quality of life than 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 can result in more long-term disabilities such as paralysis, and that this study 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, it agreed that the 13% decrement in health-related quality of life applied by the company was a reasonable assumption.

4.11 The committee considered the mortality rates the company applied in the model. 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 the monthly mortality rate applied in the model was too high; it was not their experience that patients whose neuroblastoma relapses would die within 20 months. The committee was also aware that the company applied a general population mortality ratio

of 1 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 health state 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. However, it was aware that neither the company nor the ERG identified any alternative value. The committee also concluded that the general population mortality ratio applied to the stable health state was too low. Therefore, using an annual standardised mortality ratio of 5.6 for the stable health state as applied by the ERG was a reasonable approach.

4.12 The committee discussed the administration costs of dinutuximab and interleukin-2 applied by the company in the model. In the original analysis, 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 extra days that patients are hospitalised when having the dinutuximab regimen. The committee concluded that it was not appropriate to apply the same administration costs to dinutuximab, interleukin-2 and topotecan.

4.13 The committee heard from the company that the data on the hospital days from ANBL0032 given to the ERG during clarification were incorrect because the data represented patients who had been hospitalised because of infection. The committee was aware that the company submitted additional evidence for the correctly

analysed patient population from ANBL0032, which showed that the mean number of hospital days for patients without infection was 35 days. The committee concluded that the figure of 35 hospital days was a more reasonable estimate than 69 days for a patient with neuroblastoma having treatment with the dinutuximab regimen because it was from the correctly analysed data for ANBL0032.

4.14 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 for an elective inpatient stay for treating brain tumours used by the company and adjusted to reflect the paediatric population in scenario 2 of the ERG's original report using code PM42A could be considered the most relevant for patients having dinutuximab. However, at the second appraisal committee meeting, the clinical experts stated that the NHS reference cost of an elective inpatient stay for treating paediatric brain tumours was too high because it involved high-intensity chemotherapy in an intensive care unit. The committee noted that in its revised analysis, the company chose the lower cost for an elective inpatient stay for the treatment of brain tumours or cerebral cysts (AA24C), which it had previously presented in response to clarification questions. However, the committee did not consider this code appropriate because it was not specific to a paediatric population. The committee noted that several clinical experts provided a variety of hospitalisation codes and estimates of costs from their own trusts, which would be appropriate for the administration of dinutuximab. The committee note that the ERG, in its exploratory analyses, had used the reference costs for PM43C using the 2013–14 reference costs, which were approximately £994 per day, because this more closely reflected the time-frame of the other costs referenced in in the company's model. The committee noticed that the PM43C code had been replaced in 2016–17 with a

new code PA43B, which gives a cost of £2,600 per 7-day admission plus £288 for additional days. This resulted in a lower average per day cost, which would reduce the ICER for dinutuximab compared with isotretinoin. However, the committee noted that the ERG did a scenario analysis in which it assumed that the cost of administration for dinutuximab was £0. In this case, using the company's revised base case and with the patient access scheme discount applied, the ICER for dinutuximab compared with isotretinoin remained above the usual threshold for cost effectiveness. The committee concluded that PM43C using the 2013–14 reference costs was the most appropriate hospitalisation code in the absence of a specific code for the treatment of neuroblastoma, but even when the lowest cost code was used, the ICER was still not within the range normally considered cost effective.

4.15 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. It 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. It noted that the ERG's exploratory analyses had applied a weighted average for body surface area to account for the additional vials needed for these patients. The committee concluded that this was the right approach to adjust the cost-effectiveness estimates to account for the extra vials needed for patients with a body surface area greater than 1 metre^2.

4.16 The committee discussed whether a non-reference-case discount rate of 1.5% should be applied to the costs and benefits. It 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 The committee noted the Kaplan–Meier curves in ANBL0032 showed a levelling off in event-free survival that was evident in both arms at approximately 8 years and at approximately 10 years for overall survival. The data suggested an event-free and overall survival advantage for dinutuximab over isotretinoin alone. The ERG's interpretation of this, which the committee and the clinical experts shared, was that a proportion of patients with neuroblastoma remain event free beyond year 8 and a proportion of patients can be considered to be cured of the disease. The committee heard from the clinical experts that although relapse after 10 years of event-free survival was not impossible it was very unlikely, meaning that patients who remain event free at 10 years are likely to be so for the rest of their lives. The committee also heard from clinical experts that patients who survived

neuroblastoma would not be likely to return to full health. The committee also understood that extending event-free survival meant that people whose disease relapses later tend to have a better response to subsequent therapies than those whose disease relapses sooner, and that this could translate into an overall survival advantage. The committee was aware that the company's revised base-case ICER includes the lower discount rate of 1.5% for outcomes and costs. The committee concluded that the non-reference case discount rate could apply because the 2014 analysis showed that the dinutuximab regimen could be considered to cure neuroblastoma in a small proportion of patients.

4.18 The committee considered whether the dinutuximab regimen could be considered an innovative treatment. It heard from the company that this was the first immunotherapy licensed for maintenance treatment of high-risk neuroblastoma. 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. It 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 patient experts emphasised that there is no incentive for companies to invest in treatments for paediatric cancers because these cancers are rare and the patient population is usually small. The committee appreciated the view of the patient experts, although it noted that the company was not involved in the development of dinutuximab and became involved at a relatively late stage in the marketing of the product after completion of

ANBL0032. 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. 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 are uncaptured health-related benefits. These include 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. It 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 discussed whether it would be feasible to quantify these additional benefits and incorporate them in the company's model. The committee was aware that some cost-effectiveness studies have attempted to account for uncaptured quality-of-life benefits in economic analyses. 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 concluded that even if the uncaptured health-related benefits had been quantified, the ICER for dinutuximab compared with isotretinoin would likely remain

above the usual cost-effectiveness threshold with the patient access scheme discount applied.

4.20 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's final Cancer Drugs Fund technology appraisal process and methods.

4.21 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. It noted that this was similar in the mifamurtide appraisal, and in that case special considerations for end-of-life were not applied. The committee heard from the company that children and young adults with cancer typically live longer than adults with cancer. so the 2-year life-expectancy threshold was arbitrary, unfair and biased against children. The committee referred to the advice in the NICE guide to the methods of technology appraisal (updated 2013), which is clear on how the end-of-life criteria should be applied. The committee concluded that according to the guide, dinutuximab does not fulfil the criterion for short life expectancy.

4.22 The committee considered the criterion for extension to life. It noted that, in the revised company's base case comparing the dinutuximab regimen with isotretinoin alone using the non-reference discount rate of 1.5% for costs and benefits, 4.86 life years were gained (approximately 58.3 months). Using the committee's preferred assumptions, 2.81 life years (approximately 33.7 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, so that criterion was met.However,

based on the discussion in section 4.21, the committee concluded that dinutuximab did not fulfil all the criteria required for special consideration under the supplementary advice from NICE.

4.23 The committee concluded that the dinutuximab regimen represents a novel approach as a maintenance therapy for treating high-risk neuroblastoma. The dinutuximab regimen appears to confer a small event-free survival advantage and overall survival advantage compared with isotretinoin, but the size of these benefits remains uncertain. Furthermore, the committee considered the following to be the committee's preferred assumptions based on the evidence presented:

- a 1.5% discount on costs and benefits (see section 4.17)
- a 5.6 mortality ratio for stable health (see section 4.11)
- the 2014 data cut from ANBL0032 (see section 4.8)
- Kaplan–Meier observed values from ANBL0032 for event-free and overall survival (see section 4.3)
- a cure threshold of 10 years(see section 4.9)
- a weighted average of 4.2 dinutuximab vials per treatment course (see section 4.15)
- 35 hospital days based on hospitalisation data from ANBL0032 (see section 4.13) and
- using PM43C (using 2013–14 reference costs), the hospital code rate for paediatric neoplasms with no comorbidities (see section 4.14).

The resulting ICER for the dinutuximab regimen compared with isotretinoin, based on the evidence available, was £88,100 per QALY gained without the patient access scheme discount applied. The ICER with the patient access scheme discount remained considerably above the range usually considered cost effective. The committee considered that a case remains 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 it 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 cannot not be recommended for treating high-risk neuroblastoma in patients of 1–17 years, whose disease has at least partially responded to induction chemotherapy, myeloablative therapy and autologous stem cell transplant.

4.24 The committee discussed the new arrangements for the Cancer Drugs Fund recently agreed by NICE and NHS England, noting the addendum to the NICE process and methods guides. The committee understood that, because of the timing of this appraisal, the company had not had an opportunity to present a case for including dinutuximab in the Cancer Drugs Fund. However, the committee heard from the company that dinutuximab could be considered for funding through the Cancer Drugs Fund. The committee considered that the most plausible ICER for dinutuximab (see section 4.23) was substantially higher than the range normally considered a cost-effective use of NHS resources, and so dinutuximab did not have the plausible potential for satisfying the criteria for routine use. The committee also considered that the uncertainties in the evidence from ANBL0032 were unlikely to mature within the 2-year time period specified in the addendum to the NICE process and methods guides. The committee concluded that dinutuximab did not meet the criteria to be considered for use in the Cancer Drugs Fund.

4.25 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in

particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

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 of 1–17 years whose disease has at least partially responded to induction chemotherapy, myeloablative therapy and autologous stem cell transplant. The committee concluded that a small proportion of patients having the dinutuximab regimen remain event free and that the regimen may be associated with an overall survival benefit, although the size of these benefits is uncertain. The ICER for the dinutuximab regimen compared with isotretinoin, based on the evidence available, was £88,100 per QALY gained without the patient access scheme discount applied. The committee considered that a case remains 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 it to recommend the dinutuximab regimen, even when taking into account other aspects of health-related quality of life not adequately captured in the QALY.		1.1, 4.4, 4.23
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.	4.1
	The development and availability of new treatment options is very important to patients and their families and carers.	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 a small proportion of patients having dinutuximab remain event free and that dinutuximab may be associated with an overall survival benefit, although the size of these benefits is uncertain.	4.4
	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. It also concluded that most of the innovation and development was done by the Children's Oncology Group before the company become involved in the marketing of dinutuximab.	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 of 1–17 years, whose disease has at least partially responded to induction chemotherapy, myeloablative therapy and autologous stem cell transplant.	4.24
Adverse reactions	Adverse reactions with dinutuximab could be severe, but the effects stopped when treatment ended.	4.5
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The company's clinical-effectiveness data were from the ANBL0032 trial, an international, multicentre, partially randomised study. This trial was stopped early 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. Follow-up analysis was 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.	4.3
Relevance to general clinical practice in the NHS	n/a	

Uncertainties generated by the evidence	The committee concluded a small proportion of patients having dinutuximab remain event free and that it may be associated with an overall survival benefit, although the size of these benefits is uncertain.	4.4
	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.	4.6
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No relevant subgroups were identified.	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee concluded that a small proportion of patients having dinutuximab remain event free and that it may be associated with an overall survival benefit, although the size of these benefits is uncertain.	4.4
Evidence for cost effectiveness		
Availability and nature of evidence	The company used data from the 2014 analysis of ANBL0032 to form its revised base-case economic model. The committee concluded that the 2014 analysis was appropriate for the economic modelling of the dinutuximab regimen compared with isotretinoin.	4.8
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 cured and their health follows that of the general population. The committee noted that the evidence showed that there were further events in ANBL0032 after 5 years, especially in the immunotherapy arm. It 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.	4.9
	The committee concluded that the mortality rate applied by the company to the failure health state was too high. However, it was aware that neither the company nor the ERG identified any alternative value. The committee also concluded that the general population mortality rate applied to the stable health state was too low. Therefore, using an annual standardised mortality rate of 5.6 for the stable health state as applied by the ERG was a reasonable approach.	4.11

	The committee concluded that PM43C using the 2013–14 reference costs was the most appropriate hospitalisation code in the absence of a specific code for the treatment of neuroblastoma, but that the choice of hospitalisation code had little impact on the ICER.	4.14
	The committee concluded that 35 hospital days was a reasonable estimate for a patient with neuroblastoma having treatment with the dinutuximab regimen because it was from the correctly analysed data for ANBL0032.	4.13
	The committee concluded that the non-reference case discount rate could apply because the dinutuximab 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.	4.17
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 the company had found. 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, it agreed that the 13% decrement in health-related quality of life applied by the company was a reasonable assumption.	4.10
	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. . However, even if the uncaptured health-related benefits had been quantified, the ICER for dinutuximab compared with isotretinoin would likely remain above the usual cost-effectiveness threshold with the patient access scheme discount applied.	4.19
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 data cut and analysis (2009 or 2014) from the ANBL0032 study, the cure threshold applied (5 or 10 years), the discount rate applied (3.5% or 1.5% for costs and benefits), and the administration costs used for dinutuximab and interleukin-2.	4.8, 4.9, 4.12 and 4.17
Most likely cost-effectiveness estimate (given as an ICER)	The committee noted that when its preferred assumptions were applied, using the evidence presented by the company, the resulting ICER for the dinutuximab regimen compared with isotretinoin, based on the evidence available, was £84,400 per QALY gained without the patient access scheme applied. The ICER with the patient access scheme discount remained considerably above what is usually considered cost-effective. The committee considered that a case remains 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 it to recommend the dinutuximab regimen, even when taking into account other aspects of health-related quality of life not adequately captured in the QALY.	4.24
Additional factors taken into account		
Patient access schemes (PPRS)	The company has agreed a patient access scheme with the Department of Health. If dinutuximab had been recommended, this scheme would provide a simple discount to the list price of dinutuximab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The ICER with the patient access scheme discount remained considerably above what is usually considered cost effective.	4.23
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.	4.21, 4.22
Equalities considerations and social value judgements	No equality issues were raised during the appraisal.	

Cancer Drugs Fund	The committee considered that the most plausible ICER for dinutuximab (see section 4.23) was substantially higher than the range normally considered a cost-effective use of NHS resources, and so dinutuximab did not have the plausible potential for satisfying the criteria for routine use. The committee also considered that the uncertainties in the evidence from ANBL0032 were unlikely to mature within the 2-year time period specified in the addendum to the NICE process and methods guides. The committee concluded that dinutuximab did not meet the criteria to be considered for use in the Cancer Drugs Fund.	4.24

5 Review of guidance

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

Gary McVeigh
Chair, appraisal committee
July 2016

6 Appraisal committee members and NICE project team

Appraisal committee members

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

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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