The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

**ADVICE:** following a full submission assessed under the ultra-orphan process

**dinutuximab beta (Qarziba®)** is accepted for use within NHSScotland.

**Indication under review:** for the treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with history of relapsed or refractory neuroblastoma, with or without residual disease. Prior to the treatment of relapsed neuroblastoma, any actively progressing disease should be stabilised by other suitable measures.

In patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first line therapy, dinutuximab beta should be combined with interleukin-2.

Comparisons with historical controls indicate that dinutuximab beta plus isotretinoin with and without aldesleukin (interleukin-2) improved event-free survival and overall survival in patients undergoing first-line treatment for high-risk neuroblastoma and improved overall survival in patients with relapsed neuroblastoma. In patients with relapsed or refractory neuroblastoma dinutuximab beta in combination with isotretinoin and aldesleukin was associated with tumour responses.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of dinutuximab beta. This advice is contingent upon the continuing availability of the PAS in NHSScotland or a list price that is equivalent or lower. This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chairman, Scottish Medicines Consortium

Published 12 November 2018
Indication

For the treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with history of relapsed or refractory neuroblastoma, with or without residual disease. Prior to the treatment of relapsed neuroblastoma, any actively progressing disease should be stabilised by other suitable measures. In patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first line therapy, dinutuximab beta should be combined with interleukin-2.1

Dosing Information

Intravenous (IV) infusion of dinutuximab beta 100mg/m² per cycle for five consecutive 35-day cycles. A cycle may be given as:

• a continuous infusion over the first ten days (total of 240 hours) at daily dose of 10 mg/m²; or
• five daily infusions of 20 mg/m² administered over eight hours, on the first five days.

When aldesleukin (interleukin-2) is combined with dinutuximab beta, it should be administered as subcutaneous (SC) injections of 6×10⁶ international units/m²/day, for two periods of five consecutive days, resulting in an overall dose of 60×10⁶ international units/m² per course. The first five-day course should start seven days prior to the first infusion of dinutuximab beta and the second five-day course should start concurrently with dinutuximab beta infusion (days one to five of each dinutuximab beta course).

Prior to starting each treatment course, the following clinical parameters should be evaluated and treatment should be delayed until the patient has adequate pulse oximetry, bone marrow, renal and hepatic function. Dose modifications to manage adverse events are detailed in the summary of product characteristics (SPC).

Product availability date

Dinutuximab beta is an EMA designated orphan medicine. Dinutuximab beta meets SMC ultra-orphan criteria.

Background

Dinutuximab beta is an antibody directed against the carbohydrate moiety of disialoganglioside 2 (GD2), which is overexpressed on neuroblastoma cells. After binding to GD2, dinutuximab beta induces cell death through complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity. Dinutuximab beta is licensed for use in two groups of patients: (1) those who had at least a partial response to first-line chemotherapy for high-risk neuroblastoma and subsequently completed myeloablative therapy with stem
cell transplant; and (2) those with refractory or relapsed neuroblastoma.¹ Dinutuximab beta is the second immunotherapy licensed for treatment of neuroblastoma, but is the only one currently marketed in the UK as the European marketing authorisation for dinutuximab alpha (Unituxin®), has been withdrawn.² Dinutuximab beta is an EMA designated orphan medicine for the treatment of neuroblastoma.³

Dinutuximab beta for use in this indication has been considered by SMC using its decision-making framework for the assessment of ultra-orphan medicines.

**Nature of condition**

Neuroblastoma is an embryonal tumour of the autonomic nervous system. It is thought that the cell of origin is a developing incompletely committed precursor cell from neural-crest tissues. Neuroblastomas usually occur in very young children with median age at diagnosis of 17 months. The tumours are found in sympathetic nervous system tissues, typically in the adrenal medulla or paraspinal ganglia and can present as mass lesions in the neck, chest, abdomen, or pelvis. They vary greatly in clinical presentation and prognosis. Some tumours are associated with substantial morbidity, while other spontaneously and completely regress. Age at diagnosis is considered a surrogate for underlying biologic characteristics, with tumours in younger patients more likely to have a benign course. The International Neuroblastoma Risk Group (INRG) classification system categorises tumours as very low risk, low risk, intermediate risk or high risk based on the following prognostic factors: age at diagnosis (two cut-offs: 12 and 18 months), INRG tumour stage (L1, L2, M, MS), histologic category, grade of tumour differentiation, DNA ploidy (hyperploidy/diploidy), v-myc myelocytomatosis viral related oncogene (MYCN) oncogene status (amplified or not) and aberrations at chromosome 11q (presence/absence).⁴ Dinutuximab beta meets SMC ultra-orphan criteria for the treatment of high risk and refractory or relapsed neuroblastoma.

A patient and clinician engagement (PACE) meeting was held to consider the added value of dinutuximab beta in the context of treatments currently available in NHSScotland. At the PACE meeting, attention was drawn to the fact that neuroblastoma is predominately diagnosed in young pre-school children. High-risk and relapsed or refractory disease is associated with substantial morbidity and mortality. The tumours can present as mass lesions in the neck, chest, abdomen or pelvis, with symptoms varying by tumour location. These can include nausea, vomiting and digestive problems, bone pain and limping, weight loss, bleeding, renal impairment, respiratory distress and spinal compression leading to paralysis.

Standard treatment comprises the most aggressive regimen given to children (or adults) with cancer, which includes high-dose chemotherapy, surgery, myeloablative chemotherapy and radiotherapy. It is prolonged, intensive, debilitating and associated with substantial adverse events, some of which are potentially life-threatening. Adverse events can include frequent vomiting, hair loss, weight loss, pain, fever and neutropenia that may progress to sepsis and death. There may also be long-term effects for survivors, including hearing loss, organ dysfunction, sterility, growth and development issues and secondary malignancies.
Impact of new technology

Summary of evidence on comparative efficacy

Within the International Society of Paediatric Oncology Europe Neuroblastoma (SIOPEN) high-risk neuroblastoma (HR-NBL-1) protocol, randomisation-2 was an open-label study (APN311-302). It included patients aged less than 21 years with neuroblastoma defined as high-risk by International Neuroblastoma Staging System (INSS) stage 2, 3, 4 or 4s with amplification of MYCN or, in those aged at least 12 months, INSS stage 4 without MYCN amplification and in those aged 12-18 months, only in the presence of segmental chromosomal alterations. Patients with at least a partial response after induction chemotherapy followed by consolidation with myeloablative therapy (busulfan plus melphalan [BuMel] or carboplatin, etoposide plus melphalan [CEM]) plus stem cell transplant within nine months of induction were eligible for the maintenance phase if they had no disease progression following recovery from major transplant related toxicities and had stable white cell counts. In the maintenance phase, patients received dinutuximab beta 20mg/m²/day eight-hour IV infusion for five days every four weeks for five courses and oral isotretinoin 160mg/m²/day for 14 days every four weeks for six courses. Patients were randomised equally to receive or not receive SC aldesleukin 6x10⁶ international units/m²/day for five days (Monday to Friday) in weeks 3, 4, 7, 8, 11, 12, 15, 16, 19 and 20. The primary outcome was three-year event-free survival (EFS) from randomisation, where events were defined as disease progression or relapse, second neoplasm or death from any cause. This was assessed in the full analysis set, which comprised all randomised patients who received study treatment and had clinical report data.

At 5th September 2016 data cut-off within the respective groups with and without concomitant aldesleukin 36% (69/190) and 44% (79/180) had an EFS event. There was no significant difference between the groups for the primary outcome, with Kaplan-Meier estimates of three-year EFS of 61% and 55% in the respective groups. In the subgroup of 211 patients without evidence of disease at baseline Kaplan-Meier estimated three-year EFS in those with and without concomitant aldesleukin was 66% versus 62%, respectively. However, in the subgroup of 149 patients with evidence of disease at baseline it was 54% versus 46%, respectively. There was no significant difference between groups for overall survival, with Kaplan-Meier estimates of three-year overall survival of 69% and 64%, in the respective groups. In the subgroup without disease at baseline it was 72% and 71%, respectively. However, in the subgroup with evidence of disease at baseline it was 63% and 54%, respectively.

As the comparison in the study (aldesleukin versus no aldesleukin) is not relevant to the review of dinutuximab beta, to estimate whether addition of dinutuximab beta to isotretinoin is beneficial the European Medicines Agency (EMA) regulatory review included a comparison to historical controls, i.e. patients in SIOPEN HR-NBL-1 randomisation-1 (which compared BuMel versus CEM consolidation) who had all received isotretinoin alone during the maintenance phase. This indicated that overall survival was significantly greater with dinutuximab beta plus isotretinoin compared with isotretinoin alone, with Kaplan-Meier
estimated three-year survival of 71% and 59% in the respective groups, which was noted as a clinically relevant difference by the EMA.4

An unanchored matched adjusted indirect comparison (MAIC) was performed for dinutuximab beta plus isotretinoin ± aldesleukin (combined data from both groups in APN311-302) versus isotretinoin alone (data from isotretinoin group in COG-ANBL0032). COG-ANBL0032 compared dinutuximab alpha, (Unituxin®) plus isotretinoin versus isotretinoin alone in patients undergoing first-line treatment for high-risk neuroblastoma. It was stopped early when superiority was demonstrated for addition of dinutuximab alpha to isotretinoin. It is the pivotal study supporting dinutuximab immunotherapy as standard of care.4,5 The MAIC suggested that dinutuximab beta plus isotretinoin compared with isotretinoin alone improved overall survival, with a hazard ratio of 1.382 (95% confidence interval [CI]: 0.914 to 2.089), and EFS with HR of 1.546 (95% CI: 1.098 to 2.176).

Evidence in relapsed and refractory neuroblastoma was provided by an ongoing phase I/II study (APN311-202) and from the majority of patients in a retrospective analysis of patients treated in a compassionate use programme (APN311-303), which also included nine first-line high-risk patients. In these studies, dinutuximab beta was given as a ten-day continuous IV infusion 100mg/m² per five–week cycle (four patients in APN311-202 had a lower 50mg/m² dose over a four-week cycle). Each cycle also included SC aldesleukin 6x10⁶ international units/m²/day on days 1-5 and 8-12 and oral isotretinoin 160 mg/m²/day for 14 days starting on day 22. Tumour response rates in those with detectable disease, EFS and overall survival were secondary outcomes in both studies. These are detailed in the table 1. Data were from patients with relapsed or refractory neuroblastoma in APN311-303 and interim analysis of APN311-202 at February 2015 data cut-off.4

<table>
<thead>
<tr>
<th>Study 303</th>
<th>Study 202</th>
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<tbody>
<tr>
<td>Relapsed</td>
<td>Refractory</td>
</tr>
<tr>
<td>N=29</td>
<td>N=15</td>
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<td>1 year</td>
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<td>2 year</td>
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<td>Overall</td>
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<td>2 year</td>
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<tr>
<td>N=39 with detectable disease</td>
<td>N=33 with detectable disease</td>
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<tr>
<td>Tumour response</td>
<td>End-of-treatment</td>
</tr>
<tr>
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<tr>
<td>PR</td>
<td>9 (23%)</td>
</tr>
<tr>
<td>SD</td>
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<tr>
<td>PD</td>
<td>17 (44%)</td>
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<tr>
<td>NE</td>
<td>2</td>
</tr>
</tbody>
</table>

CR = complete response (no evidence of disease); PR = partial response (improved disease); SD = stable disease; PD = progressive disease; NE = not evaluable.

The EMA review included comparisons of pooled data from APN311-303 and 202 with historical controls and was limited to relapsed patients who were aged at least one year and had INSS stage 4 disease at initial diagnosis or non-clonal type of first relapse. One control included data from relapsed patients in an Italian Neuroblastoma Registry first diagnosed
between 1999 and 2006 and the other from relapsed patients in SIOPEN HR-NBL-1 study randomisation-1. Overall survival was significantly greater in the APN311-202 and -303 cohort (given dinutuximab beta, isotretinoin plus aldesleukin) compared with patients given isotretinoin alone in Italian Registry cohort and SIOPEN HR-NBL-1 study randomisation-1 cohort, with Kaplan-Meier estimated one-year survival of 83% versus 45% and 56%; two-year survival of 60% versus 31% and 46%; and three-year survival of 50% versus 24% and 28%, respectively.4

*Other data were also assessed but remain confidential.*

**Summary of evidence on comparative safety**

Interpretation of adverse event data from the dinutuximab beta studies is complicated by co-administration of aldesleukin, isotretinoin and medicines to alleviate adverse events, including painkillers (morphine, gabapentin, non-steroidal anti-inflammatory drugs) and anti-histamines. Also, systems for recording adverse events varied, with the phase III study APN311-302 fully recording only serious adverse events with other adverse events noted on a pre-defined list of 31 specific toxicities.4

The target of dinutuximab beta, GD2, is expressed in neurons and sensory nerve fibres.5 The adverse event profile of dinutuximab beta includes neuropathic pain and neuropathy. In APN311-303 and -202, pain assessed by parents was noted in 91% (49/54) and 88% (21/24) of patients, respectively, in cycle one and decreased to 58% (22/38) and 59% (10/17) at cycle five. In APN311-302, pain related to dinutuximab beta was reported by 63% (115/183) and 75% (138/183) of patients without and with concomitant aldesleukin respectively. Across the clinical study programme, 77% (398/514) reported pain as an adverse event. In studies APN311-303 and -202, and in the groups within APN311-302 without and with concomitant aldesleukin respectively, neurological disorders of the eye were reported by 28%, 23%, 18% and 25%; motor or sensory-related neuropathy by 9%, 5%, 7% and 14%. Most were of grade one or two severity. Across the clinical study programme 3% reported serious neurological eye disorders.4

Dinutuximab beta is also associated with hypersensitivity reactions. In studies APN311-303 and -202 infusion-associated and allergic reactions were reported by 89% and 73% of patients, respectively, with most being mild or moderate in severity. In APN311-302 skin allergies were reported by 55% and 65% of patients without and with concomitant aldesleukin, respectively. Across the study programme 63% reported a hypersensitivity reaction, with 6.7% having serious infusion-related and allergic reactions and 1.2% suffering anaphylactic reaction or shock. In studies APN311-303 and -202, and in the groups in APN311-302 without and with concomitant aldesleukin, respectively, cytokine release syndrome was reported by 56%, 36%, 27% and 35%. There was a lack of standardisation in reporting capillary leak syndrome, which was noted in 83%, 36% of patients in studies APN311-303 and -202, respectively. In the APN311-302 study the addition of aldesleukin, which is associated with capillary leak syndrome, increased the incidence from 25% to 50%. Hypoxia or respiratory failure was reported by 44% and 43% of patients in studies APN311-303 and -202, respectively. All of these adverse events decreased over the cycles. Across the study programme infections were reported by 53% of patients. In studies APN311-303 and -202,
and in the groups in APN311-302 without and with concomitant aldesleukin, respectively infection was reported by 76%, 61%, 58% and 72%.\(^4\)

**Summary of clinical effectiveness issues**

For high-risk neuroblastoma, first-line treatment begins with induction of remission using intensive chemotherapy (usually including cisplatin, etoposide, vincristine, cyclophosphamide and doxorubicin) followed by surgical resection of the primary tumour. Then consolidation of remission is attempted using myeloablative chemotherapy (e.g. BuMel or CEM) to eradicate minimal residual disease followed rapidly by rescue with stem cell transplant to repopulate the bone marrow. The subsequent maintenance phase aims to treat potential minimal residual disease and reduce risk of relapse using isotretinoin, which induces terminal differentiation of neuroblastoma cell lines, and dinutuximab, which induces cell death in neuroblastoma.\(^2\) In the UK patients with neuroblastoma previously had the option to receive this treatment within the SIOPEN HR-NBL-1 study, which is now closed.\(^6\)

Despite intensive therapy more than half of the patients with high-risk neuroblastoma relapse with a subsequent dismal long-term outcome. In the past, recurrent neuroblastoma has been treated with palliative chemotherapy and radiotherapy. More recently treatment is evolving and includes salvage chemotherapy with second-line chemotherapies with mild to modest toxicity that were not included in first-line treatment (e.g. topotecan, vincristine plus doxorubicin (TVD), temozolomide plus irinotecan (TEM/IRN) or topotecan plus cyclophosphamide). Depending on the type of relapse (local or metastatic), location of tumour and previous treatment surgery or external beam radiotherapy may be used. \(^131\)I-MIBG may be appropriate for children with MIBG avid (or MIBG positive) disease. The EMA review noted that there is rationale for a child who has responded to second-line chemotherapy and/or MIBG therapy, and now has only minimal residual disease, to receive immunotherapy with dinutuximab and isotretinoin in order to try and achieve long-term remission.\(^4\)

A statistical comparison to SIOPEN HR-NBL-1 study randomisation-1 suggested that dinutuximab beta plus isotretinoin improved three-year overall survival by about 12% compared with isotretinoin alone. The difference was considered a clinically relevant by the EMA.\(^4\) Also, in an unanchored MAIC with the isotretinoin arm of COG-ANBL0032 there was improved overall survival, with a HR of 1.382 (95% confidence interval [CI]: 0.914 to 2.089), and EFS with HR of 1.546 (95% CI: 1.098 to 2.176).

In pooled analyses of data from APN311-303 and -202 studies, response rates with dinutuximab beta were 30% to 42%, with complete responses in 8% to 18% at end of treatment. Pooled data from relapsed patients in these studies suggested improved overall survival with dinutuximab beta, isotretinoin plus aldesleukin compared with isotretinoin alone in the Italian Registry cohort and the SIOPEN HR-NBL-1 study randomisation-1 cohort, with estimated two-year survival of 60% versus 31% and 46%.\(^4\)

Dinutuximab beta was approved by the EMA under exceptional circumstances. The benefit-risk balance of dinutuximab beta in high-risk neuroblastoma was considered positive, but supporting data were not comprehensive. However, as COG-ANBL0032 had demonstrated
improved EFS and overall survival with addition of dinutuximab alpha to isotretinoin, it was considered unethical to conduct a placebo-controlled study of dinutuximab beta and the withdrawal of the marketing authorisation prevented a comparison with dinutuximab alpha (Unituxin\(^*\)).\(^4\)

All studies were limited by their open-label design. The EMA noted that the EFS endpoint is complicated by several methodological issues, including exact definition of events and methods of disease status determination. The time points at which disease status was assessed during treatment and follow-up were not strictly pre-specified. Consequently, it is not clear whether the exact time of disease progression was determined. Also, there was a high level of censoring after year two in APN311-303 and -202 and data were unreliable after this time-point. These two studies were also limited by small sample size, and APN311-303 by the retrospective data collection. Across the studies dinutuximab beta was given in combination with isotretinoin ± aldesleukin and it is not possible to determine the magnitude of treatment effect due solely to dinutuximab beta. A key limitation of all studies is the lack of a control group representative of the main alternative treatment.

There were differences in the myeloablative therapies used in APN311-302 and SIOPEN HR-NBL-1, and in in data maturity, as SIOPEN HR-NBL-1 randomisation-1 was open between 2002 and 2010, while APN311-302 was open between 2009 and 2013. Data maturity within the APN311-302 and COG-ANBL0032 groups appears more consistent. In the comparison of APN311-302 with SIOPEN HR-NBL-1 randomisation-1 the EMA noted that the cohorts seems to be balanced for the main prognostic factors (MYCN status, INSS stage at diagnosis and age at diagnosis).\(^4\) The MAIC adjusted the cohort by age, INSS stage, MYCN status and tumour response before myeloablative therapy and transplant. However, it is not clear whether differences across the cohorts in residual disease after transplant were accounted for within the MAIC. COG-ANBL0032 study excluded patients with biopsy-proven residual disease after transplant. APN311-302 included 149 patients with residual disease after transplant. The company has confirmed that patients in APN311-302 with residual disease post-transplant would not have been eligible for inclusion in COG-ANBL0032. However, it was not confirmed that data from these patients were excluded from the MAIC.

For relapsed patients the comparison of pooled data from APN311-303 and 202 studies with relevant patients from the Italian registry and SIOPEN HR-NBL-1 study randomisation-1 were also limited by differences and uncertainties in induction and consolidation treatment, baseline demographic and disease characteristics, data quality and maturity and sample size. The EMA concluded that the historical comparisons suggest an improvement in overall survival with dinutuximab beta but the magnitude of this cannot be accurately estimated.\(^4\)

In APN311-302 addition of aldesleukin to dinutuximab beta plus isotretinoin had no or limited benefit in the subgroup of patients without residual disease at baseline, but may have an effect in those with evidence of residual disease at baseline.\(^4\) Dinutuximab beta can be given without aldesleukin to patients who have achieved a complete response with first-line therapy.\(^2\) In practice where aldesleukin is not given with dinutuximab beta the results from the relevant group without aldesleukin in the APN311-302 study may provide the best estimate of treatment effect.
The smaller studies in relapsed or refractory patients (APN311-303 and 202) used continuous ten-day infusions while the phase III study in patients having first-line treatment of high-risk neuroblastoma (APN311-302) used the short eight-hour infusions over five days. There are no direct comparative data of continuous versus short infusions and their relative efficacy and adverse event profiles are uncertain. There is a lack of data on use of short infusions in patients with relapsed or refractory disease and on use of continuous infusions in patients having first-line treatment for high-risk neuroblastoma. The latter may be associated with generalisation issues for study APN311-302 as it is noted in the submission that ten-day continuous infusion using a syringe pump is the current practice in Scotland.

Clinical experts consulted by SMC considered that dinutuximab beta fills an unmet need in this therapeutic area for an immunotherapy during the maintenance phase of first-line treatment of high-risk neuroblastoma. Patients have received dinutuximab beta through the SIOPEN HR-NBL-1 study and its use in combination with isotretinoin is regarded as standard of care. The clinical experts highlighted that addition of dinutuximab beta to isotretinoin is a therapeutic advance compared to isotretinoin alone as it associated with improved EFS and overall survival. They noted that dinutuximab beta would be used as it has been in the past as standard of care. Introduction of this medicine is not expected to have service implications as experience and appropriate service provision is already available within the specialist centres where it is used.

At the PACE meeting, it was noted dinutuximab beta plus isotretinoin has been the standard of care during the final phase of treatment for high-risk neuroblastoma for several years and patients in the UK have accessed this via a clinical study that is now closed. It is likely to increase the child’s chance of survival. Prior to the routine use of dinutuximab parents would have been advised at presentation that, despite the most intensive treatment regimen given to children (or adults) with cancer, their child may only have a 1 in 4 chance of survival. Since data became available for dinutuximab physicians have been able to advise parents that the disease in moving into the realms of a potentially “curable” condition and their child could possibly have a 1 in 2 chance of survival, which gives them a greater degree of hope. PACE participants noted that children cured of neuroblastoma generally go on to have a normal childhood and return to full time education. Also, for some patients with refractory or relapsed neuroblastoma dinutuximab beta can decrease or stabilize the tumour and may prolong remission.

Other data were also assessed but remain confidential.*
Patient and clinician engagement

A PACE meeting with patient group representatives and clinical specialists was held to consider the added value of dinutuximab beta as an ultra-orphan in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:
- Neuroblastoma commonly presents in young pre-school children. Despite receiving the most aggressive treatment programme given to children (or adults) with cancer, many patients with high risk disease will not survive. The outlook for those with refractory or relapsed disease is worse.
- Patients endure on average up to two years of intensive, debilitating treatment with severe potentially life-threatening side effects.
- Parents live in fear of their young child’s death while coping with the emotional and psychological impact of caring for their child during prolonged and intensive medical treatments. The length of their child’s treatment may lead to additional stress in maintaining employment or dealing with financial issues due to loss of employment. Parents may also struggle to find time to support their other children who may be fearful and need additional support to cope with their sibling’s illness.
- Parents are usually made aware of the best available treatments via support groups on social media. To ensure that their child accesses these parents can feel pressure to fundraise or to move or travel abroad. Receiving treatment for neuroblastoma remote from the child’s home can add to the burden of disease and minimise the ability of extended family and friends to help.
- Availability of dinutuximab beta in Scotland would potentially increase the chances of survival or prolonged remission for children with high-risk or refractory / relapsed neuroblastoma. It would reassure parent’s that their child had been give the best available treatment and negate the need to fundraise, move or travel abroad.
- Over the past several years as Scottish clinicians have gained experience in the use of dinutuximab beta there have been substantial improvements in its tolerability profile such that it can be now be given to the majority of patients at home (after the first one and half doses).

Additional Patient and Carer Involvement

We received patient group submissions from Neuroblastoma UK and Solving Kids’ Cancer (Europe), both organisations are registered charities. Neuroblastoma UK has not received any funding from pharmaceutical companies in the past two years. Solving Kids' Cancer (Europe) has received 2.98% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Neuroblastoma UK participated in the PACE meeting. The key points of both submissions have been included in the full PACE statement considered by SMC.
The company submitted a cost-utility analysis comparing dinutuximab beta plus isotretinoin to isotretinoin alone for the treatment of patients with neuroblastoma. The economic analysis was conducted separately for patients who achieved at least a partial response to first-line chemotherapy for high-risk neuroblastoma and patients with relapsed or refractory (R/R) neuroblastoma. Responses from SMC clinical experts indicate the comparator is appropriate.

A cohort-based partitioned survival model was used with a short-term model (up to the point of a specified cure threshold) followed by a long-term model to extrapolate the data over the lifetime time horizon of 90 years. A cure threshold was included which was set at 5 years in the base case analysis. The model included three health states: event-free survival (EFS) or stable disease health state, failure state, and death. Patients enter the model in the EFS state and start treatment with dinutuximab beta plus isotretinoin or isotretinoin alone for a maximum of 5 cycles. Patients were aged 3.7 years and 6.1 years in the high-risk and R/R models respectively based on the mean ages in the relevant studies.

For the high-risk subgroup, the source of the clinical data was the MAIC described above which used data from the APN311-302 study for the dinutuximab beta arm and from study COG-ANBL0032 for the isotretinoin arm.4,5 The results of the MAIC suggested that dinutuximab beta plus isotretinoin compared with isotretinoin alone improved overall survival, with a HR of 1.38, and improved EFS with a HR of 1.55. KM data based on the MAIC were used until the specified cure threshold at 5 years. For the R/R subgroup, the clinical data were taken from a naïve comparison of the dinutuximab beta arm of the APN311-202 study and historical control data from HR-NBL-1 study.4 For the dinutuximab beta arm, KM data were used, then a parametric curve was applied to extrapolate the clinical data for the remainder of the short term model until the cure threshold at 5 years. Based on goodness of fit statistics and visual inspection the log-normal curve was selected. Due to the lack of data for EFS in the comparator arm an assumption was made that the absolute separation over time of the OS and EFS curves in the dinutuximab beta arm of the APN311-202 study would be the same in the comparator arm.

Beyond the cure threshold at 5 years the same assumptions were applied in both subgroups where it was assumed that patients in the EFS health state could no longer experience relapse but had a higher standardised mortality ratio than the general population of 5.6 (95% CI 4.4 to 6.9) based a published study.11 For patients alive in the failure state at 5 years the model assumed a 90% probability of death based on clinical opinion.

Utility values used in the model were based on published estimates as no quality of life data were collected in the dinutuximab beta studies. A literature search was conducted which identified relevant quality of life studies.12,13 Utility decrements from these studies were applied to age-specific population norms. For the EFS disease state a utility decrement of 12.5% was applied and for the failure state a utility decrement of 41.7% was applied. Both studies used health utility index (HUI) 2 and 3 to assess quality of life. Based on a general
population utility value of 0.96, EFS and failure health states would have utility values of 0.84 and 0.56 respectively.

Medicine acquisition costs, administration and monitoring costs were included. Monitoring costs associated with dinutuximab beta were pulse oximetry, full blood count, liver and renal function tests. Costs associated with EFS health state included outpatient visits, day-case visits, and inpatient stays. For the failure health state, costs included chemotherapy treatment (topotecan, cyclophosphamide and filgrastim) with a treatment duration of up to one year plus inpatient administration costs (5 days per cycle). End of life care and adverse event costs were also included.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the list price figures can be presented.

For the high-risk subgroup the company estimated a cost per quality-adjusted life-year (QALY) of £54,361 based on an incremental cost of £160,822 and a QALY gain of 2.958. Selected sensitivity analyses are presented in table 2 which demonstrate the results are sensitive to the time horizon and changes to the clinical data used in the model.

Table 2: Summary of sensitivity analysis results – high risk population (list price)

<table>
<thead>
<tr>
<th>Analysis</th>
<th>ICER</th>
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<tbody>
<tr>
<td>Reduce time horizon to 20 years</td>
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</tr>
<tr>
<td>Dinutuximab beta effectiveness reduced by 10%</td>
<td>£88,430</td>
</tr>
<tr>
<td>Using updated survival data (2014 data cut) for isotretinoin arm</td>
<td>£88,280</td>
</tr>
<tr>
<td>Using updated survival data (2014 data cut) for isotretinoin arm and applying cure threshold at 7 years</td>
<td>£82,137</td>
</tr>
<tr>
<td>Number of vials per administration increased by 20%</td>
<td>£65,028</td>
</tr>
<tr>
<td>Assume all patients receive dinutuximab beta by continuous infusion at a dose of 20mg/m² over 5 days instead of 10mg/m² over 10 days</td>
<td>£64,961</td>
</tr>
<tr>
<td>Mean age increased to 20 years from 3.7 years</td>
<td>£64,800</td>
</tr>
<tr>
<td>Reduce time horizon to 40 years</td>
<td>£62,543</td>
</tr>
<tr>
<td>Cure threshold applied at 10 years</td>
<td>£51,860</td>
</tr>
<tr>
<td>Discount rate of 1.5% applied to costs and QALYs</td>
<td>£34,290</td>
</tr>
</tbody>
</table>

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year

For the R/R subgroup the company estimated a cost per QALY of £43,449 based on an incremental cost of £191,131 and a QALY gain of 4.399. Table 3 shows selected sensitivity analysis which demonstrates the results are sensitive to using the pooled R/R clinical data from the 202 and 303 studies and reducing the time horizon.
Table 3: Summary of sensitivity analysis results – R/R population (list price)

<table>
<thead>
<tr>
<th>Analysis</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooling the R/R data from the APN311-202 and 303 studies</td>
<td>£71,085</td>
</tr>
<tr>
<td>Reduce time horizon to 20 years</td>
<td>£67,932</td>
</tr>
<tr>
<td>Cure threshold of 10 years</td>
<td>£61,740</td>
</tr>
<tr>
<td>Number of vials per administration increased by 20%</td>
<td>£50,752</td>
</tr>
<tr>
<td>Dinutuximab beta effectiveness reduced by 10%</td>
<td>£48,418</td>
</tr>
<tr>
<td>Increasing mean age to 17 years from 6.1 years</td>
<td>£48,095</td>
</tr>
<tr>
<td>Reduce time horizon to 10 years</td>
<td>£48,021</td>
</tr>
<tr>
<td>Discount rate of 1.5% applied to costs and QALYs</td>
<td>£29,520</td>
</tr>
</tbody>
</table>

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year

There are a number of limitations with the analysis:

- There are no comparative data presented in either subgroup to provide robust evidence of the comparative effectiveness of isotretinoin plus dinutuximab beta over isotretinoin alone. A MAIC was conducted for the high-risk subgroup and a naïve indirect comparison for the R/R subgroup but there are limitations with both these analyses meaning the cost-effectiveness results are uncertain. It is noted that comparative data are available comparing dinutuximab alpha plus isotretinoin versus isotretinoin alone (COG-ANBL0032), but only data from the isotretinoin arm of this study were used in the model. The results of the high-risk subgroup are particularly sensitive to changes in the overall survival estimates. When the effectiveness of dinutuximab beta was reduced by 10% the ICER increased to £88k. Given the limitations with the clinical data underpinning the economic model and the extensive extrapolation involved, this analysis is plausible and indicates a large degree of uncertainty in the model estimates.

- Reducing the time horizon from lifetime to 20 years increased the ICER significantly, indicating that a large proportion of the benefits are accrued beyond 20 years, which further highlights the uncertainty in the long term model estimates based on limited clinical data.

- The results are sensitive to using more recent data for the isotretinoin arm. When the 2014 dataset was used the ICER increased to £88k. The company argued using the 2010 dataset used in the base case analysis was more appropriate as it was pre-specified and no patients had crossed over to receive dinutuximab beta. However, given the lack of longer term data and the extensive extrapolation in the model it is preferable to use more recent data where possible. The crossover in the 2014 analysis was minimal with only 4% of patients in the isotretinoin arm receiving dinutuximab beta, which is unlikely to have had a large impact on the result.

- The cure threshold applied at 5 years in the model is uncertain and results in survival model estimates that appear to lack face validity. Increasing the threshold to 10 years reduced the ICER in the high-risk subgroup but increased the ICER in the R/R population. The company explained that this unusual result was due to the method used to extrapolate the data when the cure threshold was applied at 10 years. While this may be true it does not address the issue that this result is counterintuitive.

- In addition to the issues noted above, the R/R subgroup results are more uncertain as they are based on a naïve indirect comparison. However this population may also be
less relevant as most patients who relapse are likely to have received dinutuximab beta as first-line treatment and therefore would not be retreated at relapse.

### Impact beyond direct health benefits and on specialist services

Experience and appropriate service provision for administration and monitoring of dinutuximab beta are available within the specialist centres where it has been used as standard care for several years.

### Costs to NHS and Personal Social Services

The company estimated there would be seven patients eligible treatment per year. It was assumed that 95% of eligible patients would be treated resulting in six patients treated with dinutuximab beta each year.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues.

The submitting company did not estimate any costs outside the NHS.

*Other data were also assessed but remain confidential.*

### Conclusion

The Committee considered the benefits of dinutuximab beta in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as dinutuximab beta is an ultra-orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted dinutuximab beta for use in NHSScotland.

### Additional information: guidelines and protocols

The Children’s Cancer and Leukaemia Group (CCLG) Neuroblastoma Special Interest Group (SIG) issued a statement in June 2017 advising on the treatment of patients in the interim period before the next SIOPEN high-risk neuroblastoma study in Europe. This recommends induction chemotherapy followed, in those who have achieved a response, by surgery to the primary tumour then myeloablative therapy and stem cell transplant. This should be followed
by a combination of differentiation therapy (isotretinoin) and immunotherapy (dinutuximab), which is regarded as standard of care.\textsuperscript{6}

**Additional information: comparators**

There are no comparator treatments for this indication.

**Cost of relevant comparators**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dose Regimen</th>
<th>Cost per course (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dinutuximab beta</td>
<td>100mg/m(^2) per cycle for five cycles</td>
<td>114,150</td>
</tr>
</tbody>
</table>

*Doses are for general comparison and do not imply therapeutic equivalence. Cost from new product assessment form. Cost based on a body surface area of 0.5m\(^2\). Cost calculated using the full cost of vials/ampoules assuming wastage.*
References

1. EUSA Pharma Ltd. Summary of product characteristics for dinutuximab beta (Qarziba®)
7. Commercial in Confidence*
9. Commercial in Confidence*
10. Commercial in Confidence*

This assessment is based on data submitted by the applicant company up to and including 24 August 2018.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy
Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.